



## **EVIDENCE-BASED GUIDELINE: DIAGNOSIS AND TREATMENT OF LIMB-GIRDLE AND DISTAL DYSTROPHIES**

**Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Issues Review Panel of the American Association of Neuromuscular & Electrodiagnostic Medicine**

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## DISCLOSURE

Dr. Narayanaswami has received honoraria from the American Academy of Neurology (AAN) and the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM).

Dr. Weiss has served as a speaker for the AAN, AANEM, American Academy of Physical Medicine & Rehabilitation (AAPM&R), Athena Diagnostics, Nufactor, Walgreens, and Grifols Inc.; serves on speakers' bureaus for Athena Diagnostics and Walgreens; has consulted for Genzyme Corporation, CSL Behring, Questcor Pharmaceuticals, and Washington State Labor and Industries; and has received research funding support from the ALS Therapy Alliance and Northeast ALS Consortium.

Dr. Selcen has served as an editorial board member for *Neuromuscular Disorders* and has received funding for research from the National Institutes of Health (NIH).

Dr. David reports no relevant disclosures.

Dr. Raynor reports no relevant disclosures.

Dr. Carter has served as the senior associate editor for *Muscle & Nerve*, has received honoraria from the AANEM and the Canadian Association of Physical Medicine and Rehabilitation, has received funding for research from the National Institutes on Aging and the National Institute on

Disability and Rehabilitation Research, and has testified on a case regarding the use of marijuana in pain.

Dr. Wicklund has served on a scientific advisory board for Sarepta Therapeutics, has served on a speakers' bureau for Genzyme, has received grant funding from Eli Lilly, and has collaborated on research without compensation with Athena Diagnostics..

Dr. Barohn has served as a consultant or on a scientific advisory board for Genzyme, Grifols, MedImmune, and Novartis; has received honoraria from Alexion, Isis, Baxter, Sarepta, and CSL Behring; and has received funding for research from the US Food and Drug Administration (FDA) and the NIH.

Dr. Ensrud reports no relevant disclosures.

Dr. Gronseth serves as an editorial advisory board member of *Neurology Now*, is an associate editor of *Neurology*, and receives honoraria from the AAN.

Dr. Griggs consults for PTC Therapeutics (Chair of DSMB), Novartis (DSMB), Marathon Pharmaceuticals, Taro Pharmaceuticals, and Viomed (DSMB); receives funding from the NIH, the Italian Telethon (DSMB Chair), the Muscular Dystrophy Association, the Parent Project for Muscular Dystrophy, and the AAN; and receives royalties from Elsevier (for *Cecil Essentials* and *Cecil Textbook of Medicine*).

Dr. Amato has served as a consultant or on scientific advisory boards for MedImmune, Amgen, Biogen, DART, and Baxter; serves as an associate editor for *Neurology* and *Muscle & Nerve*; has received royalties from publishing from *Neuromuscular Disorders*; has received honoraria from the AAN and AANEM; and has received funding for research from Amgen, MedImmune, Novartis, the FDA, and the NIH.



## ABBREVIATIONS

AAN = American Academy of Neurology  
AD = autosomal dominant  
AE = adverse event  
ALS = amyotrophic lateral sclerosis  
AR = autosomal recessive  
BMD = Becker muscular dystrophy  
CDC = Centers for Disease Control and Prevention  
CHF = congestive heart failure  
CI = confidence interval  
CK = creatine kinase  
CMD = congenital muscular dystrophy  
CMT = Charcot-Marie-Tooth syndrome  
CyA = cyclosporine A  
DMD = Duchenne muscular dystrophy  
EDB = extensor digitorum brevis  
EDMD = Emery-Dreifuss muscular dystrophy  
EF = ejection fraction  
EM = electron microscopy  
fALS = familial amyotrophic lateral sclerosis  
FCMD = Fukuyama congenital muscular dystrophy  
FVC = forced vital capacity  
GH = growth hormone  
hIBM = hereditary inclusion body myopathy  
hIBMPFD = hereditary inclusion body myopathy with Paget disease and frontotemporal dementia  
HMERF = hereditary myopathy with early respiratory failure  
LDM = Laing distal myopathy  
LGMD = limb-girdle muscular dystrophy  
LVEF = left ventricular ejection fraction  
MEB = muscle-eye-brain disease  
MFM = myofibrillar myopathy  
MM3 = Miyoshi myopathy type III  
MR = mental retardation  
PDB = Paget disease of bone  
PIRCs = percussion-induced rapid contractions  
RAE = right atrial enlargement  
ULN = upper limit of normal  
VO<sub>2</sub> max = maximal oxygen uptake  
Wmax = maximal workload  
WWS = Walker-Warburg syndrome

## **ABSTRACT**

**Objective:** To review the current evidence and make practice recommendations regarding the diagnosis and treatment of limb-girdle muscular dystrophies (LGMDs).

**Methods:** Systematic review and practice recommendation development using the American Academy of Neurology guideline development process.

**Results:** Most LGMDs are rare, with estimated prevalences ranging from 0.07 per 100,000 to 0.43 per 100,000. The frequency of some muscular dystrophies varies based on the ethnic background of the population studied. Some LGMD subtypes have distinguishing features, including pattern of muscle involvement, cardiac abnormalities, extramuscular involvement and muscle biopsy findings. The few published therapeutic trials were not designed to establish clinical efficacy of any treatment.

**Principal Recommendations:** For patients with suspected muscular dystrophy, clinicians should use a clinical approach to guide genetic diagnosis based on clinical phenotype, inheritance pattern, and associated manifestations (Level B). Clinicians should refer newly diagnosed patients with an LGMD subtype and high risk of cardiac complications for cardiology evaluation even if they are asymptomatic from a cardiac standpoint (Level B). In LGMD patients with a known high risk of respiratory failure, clinicians should obtain periodic pulmonary function testing (Level B). Clinicians should refer patients with muscular dystrophy to a clinic that has access to multiple specialties designed specifically to care for patients with neuromuscular disorders (Level B). Clinicians should not offer patients with LGMD gene therapy, myoblast transplantation, neutralizing antibody to myostatin, or growth hormone outside of a research study designed to determine efficacy and safety of the treatment (Level R).

## INTRODUCTION

Limb-girdle muscular dystrophies (LGMDs) are a group of myopathies characterized by predominantly proximal muscle weakness (pelvic and shoulder girdles).<sup>e1</sup> Initially described as a clinical phenotype, they are now recognized as a heterogeneous group of myopathies that vary in severity and may affect persons at all ages from childhood through adulthood. In 1995, the LGMDs were classified into 2 main groups depending on the inheritance pattern: LGMD1, autosomal dominant, and LGMD2, autosomal recessive. Overlaid on this numeric division is a letter designating the order of discovery for each chromosomal locus (e.g., LGMD1A implying autosomal dominant LGMD type A; LGMD2D implying autosomal recessive LGMD type D).<sup>e2,e3</sup> With advances in molecular genetics that identify new genetic defects associated with the LGMD phenotype, this list of disorders continues to grow. Unfortunately, the literature is conflicting as to the appropriate terminology for different disorders. For example, prior to genetic discovery, and even after, various reports refer to some of these disorders as congenital myopathies, myofibrillar myopathies, hereditary inclusion body myopathies (hIBMs), distal myopathies/dystrophies, or LGMD.<sup>e4</sup> Table e-1 delineates the most recent classification of what is considered “muscular dystrophies” in adults that were included in this review.

The LGMDs are rare disorders with a combined minimum prevalence of 2.27/100,000.<sup>e5</sup> Given the wide variation in phenotypic expression of the LGMDs, establishing a clinical diagnosis is a challenge. Importantly, some of these disorders are associated with potentially serious cardiac and respiratory complications. In the evaluation of a patient with LGMD, the ideal approach is to utilize the person’s clinical presentation and narrow down the possible genotype to a few disorders. This will help both to predict the long-term prognosis and to plan further evaluation, such as muscle biopsy or blood tests to confirm the genetic defect and tests of cardiorespiratory

function. With increasingly accurate molecular diagnosis, knowledge regarding the genotype/phenotype correlations, although far from complete, is slowly advancing. Although there is some literature discussing the clinical approach to LGMDs,<sup>e6</sup> no systematic reviews of the literature or practice guidelines are available for clinicians who evaluate these disorders. This evidence-based guideline reviews the current evidence regarding the diagnosis and treatment of LGMDs.

We have classified the LGMDs by their molecular diagnosis and also discuss non–limb-girdle adult-onset myopathies that are genotypically identical to the LGMDs, such as Miyoshi distal myopathy, which is allelic to LGMD2B. In addition, other hereditary myopathies that overlap and may indeed be considered forms of LGMD (e.g., hIBMs, myofibrillar myopathies, Emery-Dreifuss muscular dystrophy [EDMD], Becker muscular dystrophy [BMD], manifesting carriers of dystrophin mutations) are included. We also review the distal myopathies. Hence, this review encompasses 3 major phenotypic dystrophies: limb-girdle weakness, humeroperoneal weakness as in EDMD, and distal weakness as in the distal myopathies. We use the terms LGMD and muscular dystrophy interchangeably to refer to the disorders reviewed in this guideline.

Duchenne dystrophy, congenital muscular dystrophy, myotonic dystrophy, and facioscapulohumeral dystrophy are not included in this guideline, as they will be discussed in forthcoming guidelines. This guideline seeks to answer the following clinical questions:

1. In a population of patients with suspected muscular dystrophy, what proportion of patients has a genetic defect confirming LGMD/distal myopathy/distal muscular dystrophy/BMD?
2. In patients with muscular dystrophy, what is the association between specific features and subtypes of these disorders, in particular ethnicity; age at onset; scapular winging; weakness, atrophy, hypertrophy, or MRI changes in the facial muscles, calf, gastrocnemius, quadriceps,

hip adductors, hip abductors, and tibialis anterior; cardiac dysfunction (arrhythmias, congestive heart failure, reduced/abnormal ejection fraction [EF], dilated cardiomyopathy, hypertrophic cardiomyopathy); respiratory dysfunction (abnormal/reduced forced vital capacity [FVC]); dysphagia; dysarthria; hoarse voice; contractures; and cognitive dysfunction? In patients with LGMD, what is the association between the degree of creatine kinase (CK) elevations and specific subtypes of these disorders, in particular CK normal, <10-fold elevation, and >10-fold elevation?

3. In patients with LGMD or distal muscular dystrophy, what is the association between specific muscle biopsy features and subtypes of these disorders, in particular rimmed vacuoles, inflammation, and inclusions?

4. How often do patients with muscular dystrophy and its specific subtypes have significant respiratory abnormalities (FVC < 50% predicted), cardiac abnormalities (EF < 50%, evidence of hypertrophic cardiomyopathy or generalized wall motion abnormality, arrhythmias, conduction defects), or bone loss (osteoporosis or bone mineral density 2.5 SD below peak bone mass, osteopenia or bone mass of 1.0–2.5 SD below peak bone mass)?

5. Are there effective therapies (medications, gene therapy, exercise, complementary and alternative therapies, orthopedic interventions, surgery) for muscular dystrophies that improve muscle strength, slow the rate of strength decline, preserve ambulation and overall function, delay time to tracheostomy ventilation, maintain healthy EF, slow cardiac mortality, preserve quality of life and activities of daily living, and delay overall mortality?

## **DESCRIPTION OF THE ANALYTIC PROCESS**

In July 2010, the American Academy of Neurology (AAN) Guideline Development Subcommittee and the American Association of Neuromuscular & Electrodiagnostic Medicine Practice Issues Review Panel (appendices e-1–e-3) formed a panel of neurologists, other physicians with relevant expertise, methodologists, and patient advocates. The MEDLINE, EMBASE, and Cochrane databases were searched from 1987 onward for relevant peer-reviewed articles in humans and in English only (appendix e-4 provides the full search strategy and terms). Through an initial search conducted in 2011 and an updated search conducted in 2013, a total of 3,246 abstracts were identified. Of those, 1,335 articles were selected for full-text review. Two panel members, working independently of each other, reviewed each of the 1,335 articles and selected 699 for final review and classification. Each final article was reviewed by 2 panel members who rated it according to the AAN 2011 criteria for classification of articles (appendix e-5), using the scheme appropriate to the clinical question. The AAN population screening evidence scheme was used for questions 1–4, and the therapeutic scheme for question 5. Where differences in article ratings occurred, a third panel member determined the ultimate rating. Recommendations were developed by a modified Delphi process, and ratings of the recommendations (appendix e-6) were linked to the strength of the evidence as per the 2011 guideline development process.<sup>e7</sup> The recommendations are made by first assigning a confidence level to the evidence relative to each outcome that is deemed important. The confidence level depends on the class of studies available. The level of confidence is high if there are 2 Class I studies and very low if there are less than 2 Class III studies. Second, transparently discussed deductive principles and inferences are used to refine the level of recommendation. For instance, a Level B recommendation may be made if deductive inferences are convincing (>80% of the panel accepts them) as long as the confidence in the evidence is at least low (2 Class III studies).

Articles with descriptions of at least 3 patients were considered for inclusion. In instances of the initial description of a disorder, rare disorders, or rare manifestations of a disorder, we included studies with fewer than 3 patients. Studies were excluded if they reported group outcomes for more than one disorder and individual disorders could not be identified within the group. Genetic testing was necessary for confirmation of all diagnoses except BMD or manifest carriers of Duchenne muscular dystrophy (DMD), for which we accepted muscle biopsy immunohistochemistry/Western blot confirmation. Most often, the initial article describing the disorder did not have the gene defect identified, and therefore the article was not classified. However, these cross-referenced articles were reviewed in conjunction with the subsequent articles delineating the gene defect to obtain details of the clinical phenotype. For all questions, we classified the evidence by specific diseases: LGMD types 1A–E and 2A–P (autosomal dominant and recessive, respectively, where the gene/protein defects are known), distal myopathies, myofibrillar myopathies, EDMD, and hIBM. Because some LGMD gene defects may cause different phenotypes, the different disorders that are associated with the same gene defect are discussed together. It is also known that some protein defects can cause more severe phenotypes presenting early in childhood with congenital muscular dystrophy with or without brain involvement. We briefly state this when applicable but do not describe these phenotypes, as they will be addressed in forthcoming guidelines. We recognize that this classification is inherently artificial, because the phenotypes may merge with time. See page 174 of this document for an index of the diseases reviewed in this guideline and the pages on which they are discussed. Table e-1 and appendices e-1 through e-6 are available herein; figures e-1 and e-2 and table e-2 are available on the *Neurology*<sup>®</sup> Web site at [Neurology.org](http://Neurology.org).

## ANALYSIS OF EVIDENCE

**Clinical Question 1: In a population of patients with suspected muscular dystrophy, what proportion of patients has a genetic defect confirming LGMD/distal myopathy/distal muscular dystrophy/BMD?**

No articles were available for disorders due to genetic defects in *DNAJB6*, *TRIM32*, *FHL1*, *MYH7*, filamin C, *VCP*, matrin-3, selenoprotein, cavin, nebulin, nesprin, *KLHL9*, and Welanders distal myopathies.

***LGMD1A (myotilin).*** This is discussed below in the section on myofibrillar myopathies.

***LGMD1B (lamin A/C, also causes autosomal dominant [AD]-EDMD).*** One Class I<sup>e5</sup> and 9 Class III studies<sup>e8-e16</sup> were reviewed. In a Class I population study of 1,105 patients with various genetic disorders of muscle, the frequency of LGMD1B/AD-EDMD was 8.8% (95% confidence interval [CI] 2.1–15.6), translating to a population prevalence of 0.2/100,000 (95% CI 0–0.4).<sup>e5</sup> In the 9 Class III studies, the frequency of laminopathy among patients with LGMD ranged from 0.9-4%. However, when looking at patients with idiopathic cardiomyopathy, mutations in lamin A/C were found in 8%–39% of cases.

***LGMD1C (caveolin-3).*** Three Class III studies<sup>e11,e13,e17</sup> were reviewed. Caveolin-3 mutations were identified in 1.3%-2.6% of patients in these series.

***LGMD1E (desmin).*** This is discussed below in the section on myofibrillar myopathies.



**LGMD2A (calpain-3).** There were 2 Class I studies<sup>e5,e18</sup> and 19 Class III studies.<sup>e11,e13,e17,e19-e34</sup>

Calpainopathies have been reported in patients of many ethnic backgrounds and from 6 continents. In a Class I study, the overall prevalence of calpainopathy among various genetic disorders of muscle was 0.6/100,000 (95% CI 0.3–0.9) and the prevalence among all LGMD cases was 18/68 or 26.5% (95% CI 16–37).<sup>e5</sup> In the other Class I study of 84 Italian patients with an unknown muscular dystrophy, 39 patients (46.4%) had calpainopathy and the prevalence was calculated to be 9.47 per million.<sup>e18</sup>

In the 19 Class III studies, calpain-3 mutations accounted for 6%–57% of the LGMD, with the majority of series reporting 18.5%–35% of LGMD being calpainopathies. LGMD2A appeared to be the most common LGMD subtype in many published series in the Netherlands, England, Italy, Bulgaria, Spain, France, Turkey, Brazil, and Japan, and constituted 28.4% of known LGMD cases in northern Italy,<sup>e17</sup> 26.5% in northern England,<sup>e5</sup> and 21% in the Netherlands.<sup>e34</sup>

**LGMD2B (dysferlin).** One Class I study<sup>e5</sup> and 11 Class III studies<sup>e10,e11,e13,e17,e19,e20,e23,e24,e28,e35,e36</sup> were reviewed. Two studies describe the same cohort,<sup>e20,e24</sup> with additional patients studied over time; therefore, the studies are reviewed together. A Class I study<sup>e5</sup> found the prevalence of dysferlin mutations to be 0.13/100,000. The total group was composed of 1,105 patients with various hereditary muscle diseases, of which LGMDs overall constituted 6.15% (68 cases). Dysferlinopathies comprised 4/68 (5.9%, 95% CI 0.3–11.5) LGMD cases. The 11 Class III studies reported a frequency of dysferlinopathy ranging from 0.6%–33% of the LGMDs.

**LGMD2C (γ-sarcoglycan).** Two Class I<sup>e5,e37</sup> and 16 Class III<sup>e10,e11,e13,e17,e19,e23,e24,e38-e46</sup> studies were reviewed. A Class I study<sup>e5</sup> found the overall prevalence of γ-sarcoglycanopathy to be 1.3

per 1 million (0.13/100,000; 95% CI 0–0.3), forming 5.9% (95% CI 0.3–11.5) of the 1,105 patients with genetic muscle diseases. Another Class I study evaluated the genetic–epidemiologic aspects of primary sarcoglycanopathies in a geographic area in northeast Italy between 1982 and 1996.<sup>e37</sup> Muscle biopsies consistent with dystrophy and normal dystrophin were included in the analysis. Thirteen of 204 patients had a gene defect in one of the sarcoglycans. Four of the 13 were found to have  $\gamma$ -sarcoglycan gene defects (2 unrelated, 2 siblings) (4/204, 2%). The LGMD2C prevalence was 1.72 per 1 million.

The frequency of  $\gamma$ -sarcoglycanopathy in the 16 Class III studies ranged from 1.3%–13.2%. In those cases selected for abnormal expression of the sarcoglycans on immunohistochemistry,  $\gamma$ -sarcoglycan mutations were felt to be responsible in 7%–21%.

**LGMD2D ( $\alpha$ -sarcoglycan).** Two Class I<sup>e5,e37</sup> and 14 Class III<sup>e10,e13,e17,e23,e24,e38-e40,e43-e48</sup> studies were reviewed. One Class I study<sup>e5</sup> found the prevalence of  $\alpha$ -sarcoglycanopathy to be 0.07 (95% CI 0–0.2) per 100,000. Another Class I study from Italy reported 7/204 (3.4%) patients as having  $\alpha$ -sarcoglycan mutations. The prevalence of LGMD2C was 3.02 per million.<sup>e37</sup> The 14 Class III studies reported  $\alpha$ -sarcoglycan mutations to be responsible for 3.3%–15% of LGMDs. Of those with reduced expression of sarcoglycans on immunohistochemistry staining, 34%–40% were deemed to be LGMD2D.

**LGMD2E ( $\beta$ -sarcoglycan).** Two Class I<sup>e5,e37</sup> and 13 Class III<sup>e10,e11,e13,e17,e20,e23,e24,e38-e40,e43,e45,e46</sup> studies were reviewed. One Class I study<sup>e5</sup> found the prevalence of  $\beta$ -sarcoglycanopathies to be 0.07/100,000.  $\beta$ -Sarcoglycanopathies comprised 2.9% of the total group of genetic muscle diseases (1,105), of which LGMD formed 6.15% (68 cases). Another Class I study evaluated the

genetic–epidemiologic aspects of sarcoglycanopathies in a geographic area in northeast Italy.<sup>e37</sup> Two unrelated patients (2/204, 1%) were found to have  $\beta$ -sarcoglycan mutations; the prevalence of LGMD2E was 0.86/1000000.<sup>e37</sup> The 13 Class III studies reported  $\beta$ -sarcoglycan mutations to be responsible for 0%–23% of LGMDs, with most reporting about 4%. Of those with reduced expression of sarcoglycans on immunohistochemistry staining, 15%–43% were deemed to be LGMD2E.

**LGMD2F ( $\delta$ -sarcoglycan).** Two Class I<sup>e5,e37</sup> and 12 Class III<sup>e10,e13,e17,e23,e24,e40,e43–e46,e49,e50</sup> studies were reviewed. Neither Class I study reported  $\delta$ -sarcoglycan mutations. The 12 Class III studies reported  $\delta$ -sarcoglycan mutations to be responsible in 0%–14% of LGMDs, and approximately 8% of those cases had reduced sarcoglycan expression on immunohistochemistry.

**LGMD2G (telethonin).** Two Class III studies were reviewed.<sup>e23,e51</sup> In one Class III study of 63 unrelated patients with myofibrillar myopathy diagnosed by demonstration of myofibrillar degradation products and ectopic expression of multiple proteins on muscle biopsy, no mutations in the gene for telethonin were found.<sup>e51</sup> In another Class III study of 140 patients with LGMD from 40 families, telethonin mutations were shown in 6 patients (4.2%) in one family (2.5%).<sup>e23</sup>

**LGMD2I (FKRP).** One Class I study,<sup>e5</sup> one Class II study,<sup>e52</sup> and 12 Class III studies<sup>e10,e11,e13,e17,e28,e32,e46,e53–e57</sup> were reviewed. The Class I study<sup>e5</sup> found the prevalence of autosomal recessive *FKRP* mutations to be 0.43/100,000 (95% CI 0.2–0.7). Mutations involving *FKRP* were demonstrated in 19.1% (95% CI 9.8–28.5) of all genetic muscle diseases (1,105), 68 (6.15%) of which were LGMD. LGMD2I formed 19% of the LGMD group. In the Class II

study, 2.0% (2/102) of consecutive unrelated German patients with persistent hyperCKemia were asymptomatic or minimally symptomatic (myalgia or fatigue), and 5.1% (5/98) of consecutive unrelated patients with LGMD2 had mutations in the *FKRP* gene.<sup>e52</sup> The 12 Class III studies found mutations in the *FKRP* gene in 4%–30% of LGMD.

***LGMD2J (titin)***. One Class III study of 25 families and 25 sporadic cases of mainly distal myopathies revealed mutations in the titin gene in 4/25 (16%) families but in none of the sporadic cases.<sup>e58</sup>

***LGMD2K (POMT1)***. One Class III study of 92 patients with evidence of dystroglycanopathy based on muscle biopsy but negative genetic testing for *FKRP* mutations demonstrated that 8 patients (8.7%) had mutations in the *POMT1* gene.<sup>e59</sup> These included the following phenotypes and distributions: Walker-Warburg syndrome (WWS) (1/8), muscle-eye-brain disease/Fukuyama congenital muscular dystrophy (MEB/FCMD) (1/8), congenital muscular dystrophy with intellectual disability (mental retardation) (CMD-MR) (3/8), and LGMD with intellectual disability (mental retardation) (LGMD-MR) (3/8).

***LGMD2L (anoctamin-5)***. Two Class III studies were identified.<sup>e60,e61</sup> In one Class III study of 64 British and German patients from 59 families with either a limb-girdle or Miyoshi myopathy phenotype without dysferlin mutations, 20 patients (31.3%) from 15 (25.4%) families had a mutation in the anoctamin-5 gene.<sup>e60</sup> In another Class III study of 101 Finnish patients with undetermined LGMD, calf distal myopathy, or CK elevations more than 2,000 IU/L, 25 patients (24.8%) were identified with anoctamin-5 gene mutations.<sup>e61</sup>

***LGMD2M (fukutin).*** One Class III study of 92 patients with evidence of dystroglycanopathy based on muscle biopsy but negative genetic testing for *FKRP* mutations demonstrated that 6 patients (6.5%) had mutations in the fukutin gene.<sup>e59</sup> These included the following phenotypes and distributions: WWS (1/6), MEB/FCMD (1/6), CMD without intellectual disability (mental retardation) (CMD-noMR) (1/6), and LGMD without intellectual disability (mental retardation) (LGMD-noMR) (3/6).

***LGMD2N (POMT2).*** One Class III study of 92 patients with evidence of dystroglycanopathy based on muscle biopsy but negative genetic testing for *FKRP* mutations demonstrated that 9 patients (9.7%) had mutations in the *POMT2* gene.<sup>e59</sup> These included the following phenotypes and distributions: MEB/FCMD (6/9), CMD with cerebellar ataxia (2/9), and LGMD-MR (1/9).

***LGMD2O (POMGNT1).*** One Class III study of 92 patients with evidence of dystroglycanopathy based on muscle biopsy but negative genetic testing for *FKRP* mutations demonstrated that 7 patients (7.6%) had mutations in the *POMGNT1* gene.<sup>e59</sup> Six of the 7 patients had MEB/FCMD and 1 had LGMD-noMR.

***BMD.*** Five Class I<sup>e5,e62-e65</sup> and 5 Class III<sup>e10,e66-e69</sup> studies were reviewed. One Class I study identified 79 patients with BMD residing in the Northern Health Region of England by searching the clinical and muscle biopsy records.<sup>e62</sup> The minimum prevalence was estimated to be 2.38/100,000. A Class I epidemiologic study in the territory of Northwest Tuscany, central Italy, estimated the incidence of BMD to be  $2.42 \times 10^{-5}$  male live births.<sup>e63</sup> Thirty-one percent of

patients with LGMD (32/103) from 29 families were found to be affected by BMD. Another Class I study examined the prevalence of BMD in a geographically isolated area of Okinawa, Japan.<sup>e64</sup> The prevalence was estimated to be  $1.82 \times 10^{-5}$  in the male population. The incidence of BMD in the period from 1957–1985 was  $3.21 \times 10^{-5}$  live-born males. However, this study may underestimate the prevalence and incidence because patients with BMD were diagnosed only on the basis of immunohistochemical analysis of muscle biopsies; Western blots were not performed. In another Class I study, 109 of 1,105 (9.9%, 95% CI 8.1–11.6) patients with inherited muscle diseases carried the diagnosis of BMD, with an estimated prevalence of 7.29/100,000 males (95% CI 5.9–8.7).<sup>e5</sup> The last Class I study analyzed 3,048 muscle biopsies processed by the National Institute of Neuroscience in Tokyo and identified 41 patients as having LGMD.<sup>e65</sup> Among those, 5 patients (12%) had BMD. Population prevalence was not provided. The 5 Class III studies reported the frequency of BMD to be 1.6%–55.6% of patients presenting with limb-girdle weakness.

***Duchenne/Becker manifesting carriers.*** Four studies, 2 Class I<sup>e5,e65</sup> and 2 Class III,<sup>e67,e70</sup> were reviewed. One Class I study<sup>e5</sup> found the prevalence of Duchenne/Becker manifest carriers to be 13/1,105 (1.2%) (95% CI 0.5–1.8), corresponding to a population prevalence of 0.43/100,000 (95% CI 0.2–0.7). In one Class I study of 3,048 Japanese patients with a diagnosis of LGMD based on clinical and histopathologic criteria, only 2 women had evidence of dystrophinopathy on immunohistochemistry.<sup>e65</sup> In one of the Class III studies, in which 201 biopsies were reanalyzed using dystrophin immunoblot, 1/4 females with unclassified congenital myopathies (25%), 1/20 females with unclassified myopathies (5%), and 5/9 females (56%) with hyperCKemia were diagnosed as being manifest dystrophinopathy carriers.<sup>e67</sup> The other Class III

study retrospectively looked at 169 Israeli families with members affected by progressive muscular dystrophy. Molecular analysis was performed on 106 DMD and 5 BMD families, with 81 available probands. The investigators were able to exclude a diagnosis of DMD/BMD on the basis of clinical symptoms and signs (49 families), or normal dystrophin on biopsy and/or the absence of linkage to chromosome X by analysis of restriction fragment length polymorphism–derived haplotypes (11 families).<sup>e70</sup>

***Emerin.*** Two Class III studies were reviewed.<sup>e10,e13</sup> In one study of 550 patients with the clinical diagnosis of childhood or adult LGMD, distoproximal myopathy, or hyperCKemia, emerin mutations were seen in 2/550 (0.4%). There were 346 patients with LGMD, for a frequency of 0.6% of all LGMD.<sup>e13</sup> Another study found 2 of 370 patients with muscular dystrophy to have genetically confirmed X-linked EDMD, for a frequency of 0.54% of patients referred with a diagnosis of LGMD.<sup>e10</sup>

***Transmembrane protein 43 (TMEM43) encoding LUMA/EDMD5.*** A Class III study of 41 patients with the EDMD phenotype identified 2 patients with the heterozygous missense mutations p.Glu85Lys and p.Ile91Val in *TMEM43*.<sup>e71</sup>

***Myofibrillar myopathies.*** The term myofibrillar myopathy (MFM) refers to a group of myopathies characterized by the following specific histologic features: (1) amorphous, hyaline, or granular material in the muscle fibers on trichrome-stained sections; (2) decreased oxidative enzyme activity in many abnormal fiber regions; (3) congophilia of the hyaline structures; (4) small rimmed vacuoles; and (5) myofibrillar degeneration on electron microscopy (EM).<sup>e51</sup> The

disorder is genetically heterogeneous. In this section we discuss all MFMs with identified genetic defects.

*Myotilin (also LGMD1A)*. One Class I study<sup>e5</sup> and 3 Class III studies<sup>e8-e10</sup> were reviewed. In a Class I population study of patients with muscular dystrophy in northern England, 1,105 cases registered and followed by the neuromuscular team at the Institute of Human Genetics, Newcastle University were studied. Diagnoses were obtained in 836 patients (75.7%). The combined prevalence of inherited myopathies was 37/100,000. LGMD comprised the fifth major category, with 68/1,105 cases, or 6.15%. No cases of LGMD1A were identified. However, 2 patients diagnosed with MFM had a mutation in the myotilin gene. This corresponds to a frequency of 0.18% (95% CI 0–0.4) of the clinic population, for a point prevalence in the population of 0.07 (95% CI 0–0.2) per 100,000.<sup>e5</sup> In a Class III study, 6/57 (10.5%) families with MFM were found to carry myotilin mutations.<sup>e9</sup> A large multicenter Class III study enrolled 370 patients with LGMD from 337 families. Genotype analysis was directed by the phenotype and muscle biopsy protein abnormalities. Of 297 patients, one was found to have myotilinopathy, for a frequency of <1%. However, because only 179/297 patients had undergone mutation analysis at the time of publication, it is possible that this number is an underestimate.<sup>e10</sup> In another Class III study, 44 families with LGMD1, 14 with LGMD2, 24 with facioscapulohumeral dystrophy, 2 with scapuloperoneal dystrophy, and 2 with unclassified autosomal dominant dystrophies were screened for myotilin gene mutations. A myotilin gene mutation was found in one Argentinian family, for a frequency of 1/58 families with LGMD (1.7%).<sup>e8</sup>



*Desmin (also LGMD1E)*. One Class I study<sup>e5</sup> and one Class III study<sup>e51</sup> were reviewed. The Class I study reported the prevalence of desminopathy to be 0.17/100,000 (95% CI 0–0.3).<sup>e5</sup> In the Class III study, desminopathy was seen in 4/63 (6.3%) unrelated patients with MFM.<sup>e51</sup>

*αB-Crystallin*. One Class III study was reviewed.<sup>e51</sup> Two of 63 patients (3%) with MFM were found to carry a mutation in *CRYAB*.

*Z-band alternatively spliced PDZ motif-containing protein (ZASP) (also known as Markesbery-Griggs distal myopathy)*. One Class III study was reviewed.<sup>e72</sup> Among 54 unrelated MFM patients without mutations in desmin, αB-crystallin, or myotilin, 11 patients (20.3%) were found to carry a mutation in *LDB3*, the gene that encodes ZASP.

*BCL2-associated athanogene 3 (BAG3)*. One Class III study was reviewed.<sup>e73</sup> Among 53 unrelated MFM patients without mutations in desmin, αB-crystallin, myotilin, ZASP, or filamin C, 3 patients (5.6%) were found to carry a mutation in *BAG3*.

***Autosomal recessive hIBM/Nonaka myopathy. Glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase (GNE) quadriceps-sparing myopathy.*** Two Class III studies were reviewed.<sup>e10,e74</sup> A large multicenter Class III study enrolled 370 patients with LGMD from 337 families. Genotype analysis was directed by the phenotype and muscle biopsy protein abnormalities. One of 297 patients was found to have a mutation in the *GNE* gene, for a frequency of <1%. However, because only 179/297 patients had undergone mutation analysis at the time of publication, it is possible that this number is an underestimate.<sup>e10</sup> In another Class III

study, 92 of 1,000 (9.2%) Persian Jewish volunteers in Israel demonstrated heterozygous mutations in the *GNE* gene and therefore carrier status for hIBM.<sup>e74</sup>

**Clinical Questions 2, 3, and 4 are addressed together in the following section because they evaluate different aspects of the phenotype of LGMD: 2. In patients with muscular dystrophy, what is the association between specific clinical features, degree of CK elevation, and subtypes of these disorders? 3. In patients with LGMD or distal muscular dystrophy, what is the association between specific muscle biopsy features and subtypes of these disorders, in particular rimmed vacuoles, inflammation, and inclusions? 4. How often do patients with muscular dystrophy and its specific subtypes have significant respiratory abnormalities (FVC <50% predicted), cardiac abnormalities (EF <50%, evidence of hypertrophic cardiomyopathy or generalized wall motion abnormality, arrhythmias, conduction defects), or bone loss (osteoporosis or bone mineral density 2.5 SD below peak bone mass, osteopenia or bone mass of 1.0–2.5 SD below peak bone mass)?**

We did not include EDMD3 and EDMD4 due to *SYNE1*/nesprin-1 and *SYNE2*/nesprin-2 mutations because there was not enough evidence for a detailed assessment of phenotypes. No studies were available evaluating bone loss in LGMD.

***LGMD1A (myotilin).*** This is discussed in the section on MFM.

***LGMD1B (lamin A/C).*** There were 47 Class III studies.<sup>e12,e15,e16,e75-e118</sup> Mutations in the *LMNA* gene result in diverse phenotypes, including LGMD1B, AD-EDMD, dilated cardiomyopathy with conduction system disease, Dunnigan type familial partial lipodystrophy, mandibuloacral

dysplasia, Hutchinson-Gilford progeria syndrome, restrictive dermopathy, and a form of dominant-intermediate Charcot-Marie-Tooth syndrome (CMT). Phenotypic variability has been reported even in kinships with the same mutation.<sup>e95,e96,e103</sup> Onset was congenital to adult life (fifth decade) with humeroperoneal (AD-EDMD) and limb-girdle phenotypes.

The AD-EDMD phenotype was characterized by proximal muscle weakness in the upper extremities with preferential involvement of humeral muscles, both proximal and distal weakness in the lower extremities, elbow and ankle contractures, and spine rigidity (cervical > thoracic and lumbar). Of note, in some series contractures were seen only late in the disease course or not at all, which is different than X-linked EDMD, in which contractures are invariably present early in the disease course.<sup>e75,e81,e88,e106,e116,e118</sup> Occasional patients had pseudohypertrophy of the calves or scapular muscles. Atrophy was appreciated in humeral muscles (biceps > triceps) and below the knees, particularly in the medial gastrocnemius.<sup>e75</sup> Scoliosis of the thoracic spine was also noted in addition to rigidity. Scapular winging was uniformly seen and was correlated with the severity of weakness.<sup>e75</sup>

The LGMD phenotype was characterized by proximal leg-greater-than-arm weakness, but often with preferential involvement of humeral muscles. Again, flexion contractures of elbows and Achilles tendons were usually minimal or developed late in the course.<sup>e106,e116,e118</sup> Cardiac abnormalities (arrhythmias, conduction defects, and dilated cardiomyopathy) were common and may be the only presenting feature of laminopathy. Pacemakers or intracardiac defibrillators were commonly implanted because of arrhythmias and the risk of sudden cardiac death. Cardioembolic stroke occurred because of associated arrhythmias. Many patients also required cardiac transplantation because of congestive heart failure (CHF) from dilated cardiomyopathy.

CK levels were normal or slightly elevated—most series had a CK average of <5 times the upper limit of normal (ULN). EMG usually revealed nonspecific myopathic features. MRI/CT demonstrated fatty infiltration in the posterior compartment of the thigh and calves.<sup>e80</sup> The medial gastrocnemius and soleus appeared to be preferentially involved in laminopathies in some studies, even in patients who had only cardiac abnormalities without muscle weakness clinically.<sup>e77,e84,e85</sup> However, other studies have found both the lateral and the medial gastrocnemius to be involved equally.<sup>e80</sup> In both AD-EDMD and LGMD1B phenotypes, other muscles that were involved included the glutei, quadriceps, adductor magnus, and hamstrings.<sup>e77,e106</sup> One study attempting to differentiate AD-EDMD and Bethlem/Ullrich myopathies (collagen VI disorders), which can also be associated with contractures, found that the quadriceps were relatively spared and the hamstrings were more severely involved in AD-EDMD.<sup>e80</sup> Muscle biopsies revealed nonspecific myopathic features (e.g., variability in fiber size with or without necrotic and regenerating muscle fibers and increased endomysial connective tissue). One series reported endomysial inflammation in young children who were initially felt to have an inflammatory myopathy.<sup>e106</sup> Biopsies have shown normal or reduced immunostaining for lamin A/C<sup>e79,e81,e83</sup> and laminin beta-1.<sup>e90</sup> Rare rimmed vacuoles were reported.<sup>e78</sup> On EM, nuclear alterations in about 10% of the preserved muscle fibers with peripheral heterochromatin loss or detachment from the nuclear envelope and interchromatin texture alterations have been reported.<sup>e113</sup>

As mentioned, mutations involving lamin A/C have also been associated with dominant-intermediate CMT (not reviewed in this manuscript),<sup>e119</sup> and some patients have signs of both a myopathy and a neuropathy on EMG and muscle biopsy.<sup>e93</sup>

***LGMD1C (caveolin-3)***. Thirteen Class III studies were reviewed.<sup>e120-e132</sup> Patients have been reported from the United Kingdom, Italy, Spain, Sweden, and Japan.<sup>e120-e122,e130,e132</sup> Age at symptom onset ranged from 5–81 years. The clinical phenotypes varied. Intrafamilial variation was not uncommon, and patterns of involvement included proximal arm and leg weakness, distal weakness, rippling muscle disease, or asymptomatic hyperCKemia. Prominent muscle cramps (spontaneous, postexercise, or myalgias) were noted in most patients.<sup>e120-e122</sup> In 3 studies, distal hand weakness and atrophy was noted in 9/23 patients.<sup>e121,e122,e132</sup> In one series, 3 of 10 patients presented with toe walking but did not have distal leg weakness.<sup>e121</sup> Rippling muscle disease was the sole manifestation of caveolinopathies in several families. One series reported generalized percussion-induced rapid contractions (PIRCs) in the face, neck, and extremities as a constant feature, but actual rippling muscles were seen less frequently (12/19).<sup>e131</sup> In a study of 23 patients from a large Swedish family, all except 2 presented with muscle stiffness.<sup>e130</sup> Percussion-induced muscle mounding and PIRC were noted in all 23 patients, muscle rippling in 12, calf hypertrophy in 9, and generalized hypertrophy in 2, whereas weakness was not observed. Rhabdomyolysis and myoglobinuria were rarely noted (1/10 patients in one study, 4/19 in another).<sup>e121,e131</sup> Most patients, even when asymptomatic, exhibited calf hypertrophy.<sup>e120,e121</sup> Six of 7 in one family had pes cavus.<sup>e122</sup> Scapular winging, facial weakness, and rigid spine were not seen. Mild contractures were seen in one study (finger flexor and hamstrings in 2/10 patients).<sup>e121</sup> CK levels were elevated 3–30 times above normal.<sup>e120-e122,e130</sup> Four of 7 patients in one family had asymptomatic hyperCKemia (2 patients subsequently developed weakness in the hands 2 decades later).<sup>e122</sup> Rare patients with cardiac involvement have been described, although clinical cardiac manifestations are distinctly uncommon.<sup>e123,e124</sup> Muscle biopsies were normal or mildly

myopathic or dystrophic, without specific diagnostic features.<sup>e121</sup> Reduced staining for caveolin-3 on the sarcolemma on immunohistochemistry has been reported.<sup>e121,e122,e130,e132</sup>

***LGMD1D (DNAJB6).*** The nomenclature of LGMD1D and LGMD1E has been confusing in the literature. AD LGMD linked to chromosome 7q36 has been termed LGMD1D as well as LGMD1E. In this guideline, we refer to 7q36-linked LGMD with mutations in the DNAJB6 protein as LGMD1D. Three Class III studies were reviewed.<sup>e133-e135</sup> Two studies describe the same Finnish families and are reviewed together.<sup>e133,e134</sup> One of the studies<sup>e134</sup> also includes 2 Italian families and 2 US families, whereas the third<sup>e135</sup> describes 2 families from the US (ethnicity not mentioned). Disease onset was in the third to sixth decade, except for 2 US patients from different families with onset at ages 14 and 18 years. All patients had moderate to severe proximal muscle weakness in the lower extremities; often the quadriceps was relatively preserved compared to the hamstrings.<sup>e135</sup> Proximal upper extremity weakness was absent or milder than lower extremity weakness. In one study, distal lower extremity weakness involving the posterior compartment more than the anterior compartment was noted in all 9 families.<sup>e134</sup> Another study reported one family in which 3 affected members had distal muscle atrophy and weakness in the legs as well as the arms and mild to moderate proximal weakness.<sup>e135</sup> Some patients had heel cord contractures. Cardiorespiratory involvement was notably absent.

Serum CK levels ranged from normal to 10-fold elevated but averaged about 2–3 times the ULN in most cases. Muscle biopsy in all studies revealed a myopathy with rimmed vacuoles, features suggestive of an MFM in 7/9 families.<sup>e134</sup>

**LGMD1E (desmin).** This is discussed in the section on MFM.

**LGMD2A (calpain-3).** One Class I<sup>e136</sup> and 36 Class III<sup>e17,e19,e22-e26,e28,e30,e33,e34,e85,e137-e160</sup> studies were reviewed. Most cases had onset between 5 and 20 years of age. The mean age at onset across studies spanned 9.8–21.8 years,<sup>e138,e149</sup> but the range was broad, from 2–65 years.<sup>e30,e33</sup> Approximately 20%–50% of patients eventually became wheelchair dependent,<sup>e136,e137,e140,e148</sup> and the mean time from disease onset to loss of ambulation ranged from 9.4–23.6 years.<sup>e140,e148</sup> Onset of weakness occurred in the lower extremities alone in 80%, in the lower and upper extremities in 13%, in the upper extremities alone in 3%, and with isolated hyperCKemia in 4%.<sup>e25,e148,e150</sup> Hip extensor, hip adductor, and knee flexor muscles were most affected.<sup>e33,e148,e149,e152,e157,e158</sup> Facial weakness was uncommon; it was reported in less than 5% of cases (4/96 cases).<sup>e25,e138,e148,e150,e152</sup> Calf hypertrophy was seen in 51/126 (40%) cases.<sup>e23-e25,e33,e148,e150,e157</sup> However, in the Class I study, calf hypertrophy was described as rare.<sup>e136</sup> Scapular winging often was not present at diagnosis but over time became nearly universal. Overall, scapular winging was present in more than 80% of patients (78/95).<sup>e24,e33,e34,e150,e152,e157</sup> Dysphagia was not present in any of 51 patients across 3 studies.<sup>e138,e148,e157</sup> Likewise, dysarthria and hoarseness of voice were seen in none of 20 patients.<sup>e148</sup> Contractures occurred in 25% (18/71) of patients and predominantly affected the ankles.<sup>e17,e30,e33,e34</sup> There was essentially no symptomatic cardiac involvement. Across all studies, 9% (17/198) of patients had abnormalities on cardiac testing. In a Class I study, 7/35 patients had ECG abnormalities.<sup>e136</sup> The abnormalities included nonspecific conduction abnormalities in 5/35 patients and repolarization abnormalities in 2/35 patients. No significant abnormalities were found in the 29 patients who underwent echocardiography.<sup>e136</sup> None of the patients in the Class I

study had cardiac symptoms. Eight Class III studies evaluated cardiac testing.<sup>e17,e25,e138,e148,e150,e152,e156,e157</sup> Five percent (8/163) of patients had ECG changes, including premature atrial or ventricular beats, ST segment elevations, atrial fibrillation, atrioventricular conduction block, or bundle branch block<sup>e25,e150,e156</sup>; 2% (4/163) had abnormalities on echocardiography, including mild anterior cardiac wall dysfunction, mildly impaired left ventricular function, slight diminution of left ventricular contractility, and a left ventricular ejection fraction (LVEF) slightly below 50%.<sup>e25,e148,e150,e156</sup> Four Class III studies found no abnormalities on ECG or echocardiography.<sup>e17,e138,e152,e157</sup> Significant respiratory involvement was very infrequent until late in the disease course. Seven percent (8/117) of patients had a restrictive pattern over multiple studies,<sup>e17,e136,e138,e150,e156,e158</sup> but 12/20 had an FVC reduced to 30%–50% of normal late in the disease course.<sup>e148</sup> Cognitive dysfunction was not reported (0/75 patients).<sup>e17,e25,e148,e157</sup>

MRI demonstrated fatty and fibrous replacement in the gluteal, hamstring, adductor, soleus, and medial gastrocnemius muscles.<sup>e85,e144,e149,e152,e155</sup> CK levels were most often more than 10 times the ULN, with a mean of 19 times the ULN and a range of normal to 110 times the ULN. CK levels were elevated >10 times the ULN in 90/146 (62%), 2–10 times the ULN in 50/146 (34%), and were normal in 6/146 (4%).<sup>e19,e22,e24,e25,e30,e33,e34,e136,e142,e152,e153,e157,e158</sup> On muscle biopsy, lobulated fibers were frequently seen: 33/47 biopsies (70%) on NADH-stained sections.<sup>e25,e26,e148</sup> Rimmed vacuoles and inclusions were not features, but inflammation, including eosinophils, may be seen on some biopsies.<sup>e30,e140,e150,e160</sup> Western blot analysis of muscle calpain-3 in patients with LGMD2A can show a total or partial deficiency or no deficiency. Furthermore, calpain-3 may be reduced in muscle from patients with LGMD2B and patients with LGMD2J,



whereas dysferlin immunostaining may be reduced on muscle biopsies from patients with LGMD2A.<sup>e150</sup> Thus, genetic testing is required to confirm all cases.

***LGMD2B/Miyoshi myopathy (dysferlin).*** One Class II study<sup>e161</sup> and 54 Class III studies<sup>e17,e23,e24,e137,e145,e147,e149,e155,e162-e207</sup> were reviewed. The mean age at onset has been reported as 18.4–31.9 years across reports, with most studies falling between 19 and 23 years. The range for age at onset was 3–60 years, with most studies describing a range of 10–35 years.<sup>e17,e23,e24,e145,e147,e149,e162-e164,e166-e168,e170,e171,e173-e176,e178,e182,e183,e185,e188-e191,e193,e195,e197,e198,e200-e205</sup> The dysferlinopathies involve 2 principal clinical phenotypes<sup>e169,e192,e200,e206</sup> that can merge over time.<sup>e167,e168</sup> The Miyoshi phenotype is characterized by distally predominant weakness principally involving the posterior compartment (calf), as described in 17/19 dysferlinopathies,<sup>e162</sup> 14/29,<sup>e163</sup> 18/25,<sup>e166</sup> 21/26,<sup>e147</sup> 9/14,<sup>e167</sup> 11/36,<sup>e168</sup> 4/8,<sup>e177</sup> 2/9,<sup>e178</sup> 46%,<sup>e188</sup> and in several other series.<sup>e165,e170,e172,e174-e176</sup> The second phenotype is characterized by a limb-girdle pattern of weakness, accounting for 15/29 dysferlinopathies,<sup>e163</sup> 3/25,<sup>e166</sup> 8%,<sup>e147</sup> 7/9,<sup>e178</sup> 23/33 (70%),<sup>e23</sup> 22/36 (61%),<sup>e168</sup> 40%,<sup>e188</sup> “most” of 37,<sup>e17</sup> and 5/14<sup>e167</sup> in various series. There can be preferential weakness of the biceps in the arms followed by lesser weakness of the deltoid and triceps<sup>e149,e163,e167,e173,e205</sup>; the weak biceps and relatively preserved deltoid can produce a “deltoid bulge.”<sup>e173</sup> Even in patients presenting with a “limb-girdle” phenotype, the gastrocnemius muscle was still notably atrophic, particularly the medial aspect.<sup>e23,e167,e168</sup> Rare patients presented with anterior leg (tibialis anterior) weakness and foot drop, occurring in 3/8,<sup>e177</sup> 2/19,<sup>e162</sup> 2/30,<sup>e188</sup> 4 cases in one family,<sup>e207</sup> and 2/11<sup>e203</sup> cases. Weakness was commonly asymmetric.<sup>e167,e168</sup> One study described a “diamond on the quadriceps” bulge, affecting 21/31 patients with dysferlinopathy who presented with both the Miyoshi and limb-girdle pattern of

weakness.<sup>e170</sup> Calf atrophy was typical,<sup>e189,e195</sup> and atrophy of the anterior shin was sometimes seen.<sup>e195</sup> Calf hypertrophy and pain have been reported early in the course in 5/29,<sup>e163</sup> 1/3,<sup>e24</sup> 3/14,<sup>e167</sup> 5/39,<sup>e23</sup> and 6/21<sup>e173</sup> patients with dysferlinopathy. Partial atrophy of the biceps has been observed in both the Miyoshi and limb-girdle phenotypes,<sup>e189</sup> and selective atrophy of the shoulder girdle muscles producing a “double calf’s head on a trophy” sign has been described.<sup>e195</sup> Scapular winging, dysphagia, dysarthria, and contractures were not reported. Some dysferlinopathy patients can present with asymptomatic hyperCKemia or recurrent myoglobinuria<sup>e192</sup>; symptomatic carriers have also been described.

Respiratory and cognitive dysfunction have not been described. Cardiac involvement was uncommon.<sup>e96,e162,e168,e178,e189,e191,e201,e205</sup> Nonspecific ECG changes have been reported in some patients.<sup>e17,e161</sup> Echocardiography has demonstrated left ventricular hypertrophy or reduced EF in rare patients.<sup>e17,e161,e204</sup> Subclinical cardiac fibrosis or diastolic dysfunction was reported in a few patients by cardiac MRI.<sup>e197</sup> Cardiac muscle biopsies in 2 patients revealed absence of dysferlin from the sarcolemma with perivascular and interstitial fibrosis.<sup>e204</sup>

Muscle CT<sup>e175,e193</sup> and MRI<sup>e149,e155,e165,e167,e172,e189,e191,e203</sup> reported preferential involvement of the posterior compartments of the distal and proximal legs. By MRI, the pattern of muscle involvement appeared similar for patients with both the Miyoshi and limb-girdle phenotypes,<sup>e189</sup> with early involvement of the gastrocnemius and thigh adductors. CK levels were typically markedly

elevated,<sup>e17,e162,e165,e167,e168,e171,e172,e173,e175,e177,e178,e182,e183,e185,e189,e191,e193,e200,e201,e204,e205,e206</sup> up to 10–30 times,<sup>e163</sup> 23–40 times,<sup>e24</sup> 36 times,<sup>e23</sup> 20–100 times,<sup>e174</sup> or 15–30 times<sup>e185</sup> the ULN.

Muscle biopsies were characterized by dystrophic changes.<sup>e145,e162-</sup>

<sup>e167,e169,e171,e173,e175,e177,e178,e181,e183,e184,e193,e201,e202,e205-e207</sup> Perivascular and/or endomysial

inflammatory infiltrates were common.<sup>e162,e164,e166,e169,e171,e173,e181,e183,e184,e187-e189,e193,e201,e202</sup>

Amyloid deposits were detected by Congo red staining in blood vessel walls and in perimysial connective tissue in one study<sup>e173</sup>; 4/6 specimens in a second study also contained sarcolemmal and interstitial amyloid deposits in skeletal muscle.<sup>e200</sup> Absence or reduction of dysferlin by immunofluorescence and/or Western blot staining was characteristic.<sup>e17,e147,e166-</sup>

<sup>e169,e176,e177,e182,e183,e192,e193,e196,e198,e200-e202</sup> Rimmed vacuoles and inclusions were not a common feature, although a single study described rimmed vacuoles in 4/14 patients with a Miyoshi phenotype.<sup>e188</sup>

***LGMD2C (γ-sarcoglycan).*** Two Class I<sup>e208,e209</sup> and 15 Class III<sup>e17,e23,e41,e43,e210-e220</sup> studies were reviewed. This dystrophy occurs worldwide but may be more common in Roma/Gypsy<sup>e209,e216</sup> and Tunisian populations.<sup>e208,e220</sup> Onset occurred in the early childhood to adult years, but most series had an age at onset in early childhood, with a range of 1–13 years (mean 6.1 years) in one Class I study<sup>e208</sup> and a range of 2–8 years in the other Class I study.<sup>e209</sup> However, other series had slightly later ages of onset, ranging from 2–23 years (mean of ~11 years).<sup>e17,e23</sup> Patients presented with proximal leg weakness greater than proximal arm weakness. Scapular winging, calf hypertrophy, macroglossia, ankle contractures, and scoliosis were common, at least in the Roma populations with the disorder.<sup>e209,e216</sup> Age at loss of ambulation ranged from 11–37 years (mean 16 years) in one Class I study<sup>e208</sup>; 81% of patients were wheelchair dependent by age 14 years in the other Class I study.<sup>e209</sup> Normal intelligence was noted in 2 small series.<sup>e41,e215</sup> The largest series of 68 patients with LGMD2C found no patient with clinically relevant cardiomyopathy.<sup>e216</sup> Most small studies reported that patients had normal ECG and echocardiography.<sup>e41,e210,e218</sup> In one study, ECG and echocardiogram were normal in 2/3 patients

and revealed abnormal contraction of the interventricular septum in 1/3<sup>e217</sup>; 4/10 patients had dilated cardiomyopathy in another study.<sup>e211</sup> Ventilatory muscle weakness requiring noninvasive ventilation developed in 2/5,<sup>e217</sup> but respiratory function was normal in other small series.<sup>e43,e215</sup> CK levels were elevated 4–100 times normal in most series.<sup>e17,e23,e208,e211-e213,e216</sup> Muscle biopsies revealed markedly reduced or absent  $\gamma$ -sarcoglycan on immunohistochemistry, whereas immunohistochemistry of other sarcoglycans was more variable (normal or moderately reduced).<sup>e23,e208,e210,e211,e212,e216,e219</sup>

***LGMD2D ( $\alpha$ -sarcoglycan).*** Eighteen Class III studies were

reviewed.<sup>e17,e19,e23,e43,e145,e149,e156,e164,e213,e218,e219,e221-e227</sup> LGMD2D has been described in French,

Italian, Moroccan, Algerian, Finnish, German, white Brazilian, and African-Brazilian

families.<sup>e19,e23,e221,e223,e225,e226</sup> Symptom onset occurred at 1–30 years of age (mean 10.5 years).

The legs were weaker than the arms. The glutei and hip adductors were involved more than the psoas and the thigh muscles; the quadriceps and hamstrings were involved equally. Distal lower extremity weakness was minimal and, if present, involved the tibialis anterior. In the upper extremity, the deltoids, serratus anterior, trapezius, and latissimus dorsi and rhomboids were involved early. The infraspinatus was affected more than the supraspinatus, and the biceps was involved but less so than the infraspinatus and supraspinatus; the triceps, pronators, and supinator were spared. Trunk extensors were involved but neck flexors only minimally so.

Scapular winging, thigh atrophy, and calf hypertrophy were seen in the majority of patients across studies.<sup>e213,e221,e223</sup> The weakness varied widely in severity, and intra-/interfamilial

variation was common. In one study, 4/24 patients lost ambulation before age 16, whereas 9 were ambulatory, 3 of whom were aged 50 or older (age range 6–56 years, mean 34.4 years,

although the 2 youngest patients had been followed only 1 and 3 years).<sup>e213</sup> Intellectual development was noted to be normal in all 12 cases in one study.<sup>e226</sup> CK levels were elevated in all patients but varied widely from 2–100 times normal.<sup>e17,e19,e23,e213,e221,e223,e227</sup> Symptomatic cardiomyopathy was not common, at least early on. ECG revealed nonspecific abnormalities in a minority of patients.<sup>e156</sup> Echocardiography was usually normal,<sup>e156,e213</sup> although a minority had findings of a dilated cardiomyopathy.<sup>e218,e226</sup> Severe ventilatory muscle weakness has been reported in up to one-third of patients.<sup>e43,e213</sup> CT scan of the lower limbs revealed early involvement of pelvic muscles, especially the glutei and posterior and deep anterior thigh muscles.<sup>e221</sup> The medial femoral muscles were spared in the mildly affected patients. Hypertrophy of rectus femoris, sartorius, and gracilis was observed in a mildly affected patient. Distal muscles were spared except in the severe cases, when the tibialis anterior was involved. Muscle MRI in 2 patients demonstrated more severe involvement of the quadriceps than the posterior thigh muscles, with hypertrophy of the gracilis and sartorius; one of these patients also had changes in the soleus, gastrocnemius, and peroneus longus.<sup>e149</sup> Muscle biopsies revealed variable immunohistochemistry staining of the sarcoglycan complex.<sup>e219,e225,e226</sup>

***LGMD2E ( $\beta$ -sarcoglycan).*** Thirteen Class III studies were

reviewed.<sup>e17,e23,e24,e40,e43,e144,e156,e164,e213,e219,e228-e230</sup>  $\beta$ -Sarcoglycanopathy was reported in patients of Turkish, Italian, East Indian, Tunisian, white Brazilian, and African-Brazilian descent.<sup>e17,e23,e24,e40,e228,e229</sup> The age at onset was 8–20 years (mean 6.9 years).<sup>e17,e40,e213</sup> Clinical features varied, including mild proximal muscle weakness (pelvic > shoulder girdle) in 6/12 patients and asymptomatic hyperCKemia with calf hypertrophy in 2/12 patients in one study, but

a severe DMD-like picture was noted in 30%–70% of cases across reports.<sup>e23,e24,e213,e228</sup> Loss of ambulation and wheelchair dependence was variable and seen in childhood or early adulthood.<sup>e23,e40,e229</sup> Patients may have calf hypertrophy<sup>e24,e213,e228</sup> or scapular winging.<sup>e24</sup> Spinal scoliosis and Achilles contractures were rare.<sup>e229</sup> The type and severity of cardiac involvement varied across studies. Normal cardiac function was reported in some studies.<sup>e24,e213,e228</sup> However, cardiomyopathy was apparent by echocardiogram in some studies.<sup>e40,e43,e230</sup> One patient died at age 21 of cardiac arrest in one series.<sup>e23</sup> Respiratory function was stated to be normal in all 12 patients in the Turkish study, although details were not mentioned.<sup>e228</sup> However, some patients developed ventilatory failure over time.<sup>e43,e156,e213</sup>

CK levels were elevated 2–110 times normal (mean 14 times) across studies.<sup>e17,e23,e213</sup> Muscle imaging in one patient revealed severe fatty atrophy of the shoulder and pelvic girdle.<sup>e144</sup> Muscle biopsies revealed typical dystrophic features along with variable immunohistochemical staining to the sarcoglycans. A complete absence of immunohistochemical staining tended to be associated with earlier onset in one study<sup>e17</sup> and more severe phenotype in 2 studies.<sup>e213,e219</sup>

***LGMD2F ( $\delta$ -sarcoglycan).*** Eight Class III studies were reviewed.<sup>e17,e23,e40,e43,e44,e213,e219,e231</sup> Two of these studies had only one patient with LGMD2F each because they studied sarcoglycanopathies as a whole, but they were included because of the rarity of the disorder.<sup>e17,e213</sup> The Brazilian studies<sup>e23,e43,e219,e231</sup> appear to describe the same patients, with a few additional patients in the later papers, and are reviewed together. The ethnicity of the described patients was East Indian, white Brazilian, and African-Brazilian.<sup>e23,e40</sup> The age at onset was 4–10 years.<sup>e17,e23,e213,e231</sup> Eight of 9 patients had a severe DMD-like presentation with onset in early childhood and wheelchair dependence between 11 and 16 years. One patient was ambulatory for

short distances at 19 years.<sup>e23,e231</sup> Two patients, one aged 13 years and the other aged 17 years, also had a DMD-like presentation with cardiac involvement (one presymptomatic cardiomyopathy and pulmonary hypertension, one dilated cardiomyopathy). Respiratory involvement was noted in both patients (one mild, FVC 76%; one moderate, FVC 54%).<sup>e43</sup> CK levels were elevated 5–24 times normal, with a 100-fold elevation in one case.<sup>e23,e40,e43,e213</sup> Immunohistochemical analysis revealed total absence of all sarcoglycans in 3 patients and absence of  $\alpha$ -,  $\beta$ -, and  $\delta$ -sarcoglycan with partial deficiency of  $\gamma$ -sarcoglycan staining in one patient.<sup>e44,e219</sup>

***LGMD2G (telethonin).*** Three Class III studies were reviewed.<sup>e23,e232,e233</sup> The family described in one of the studies<sup>e23</sup> was also included in another study.<sup>e232</sup> The initial description by the same authors was cross-referenced to obtain details of phenotype. Twelve patients from 3 Brazilian families were described. Onset was between 2 and 15 years. Patients had lower extremity distal-greater-than-proximal or proximal-greater-than-distal weakness. In the upper extremities, the weakness was more proximal than distal. Progression of the disease varied within families. Calf hypertrophy was seen in all affected patients of one family. CK levels were elevated from <10 to 30 times normal. Cardiac involvement was noted in 3/6 affected members of one family; the type of involvement was not specified. Muscle biopsy was remarkable for abundant rimmed vacuoles in 2 families.<sup>e233</sup>

***LGMD2H/TRIM32/sarcotubular myopathy.*** Four Class III studies were reviewed.<sup>e234-e237</sup> The initial families were of Hutterite descent.<sup>e234,e237</sup> The age at onset ranged from birth to the seventh decade of life. Most affected individuals had a limb-girdle pattern of weakness. Facial

weakness, scapular winging, calf hypertrophy, Achilles contractures, neck flexor weakness, and exercise-induced myalgias were noted in a few patients (2/5,<sup>e234</sup> 2/4,<sup>e235</sup> 1/4<sup>e236</sup>); neck flexors were weak and tendo Achilles contractures were noted in 2/4 patients.<sup>e234-e236</sup> Peripheral neuropathy with slowed nerve conduction velocity was seen in 3/5 patients in one study.<sup>e235</sup> ECG in 9 patients showed right bundle branch block in 2.<sup>e235,e236</sup> Respiratory function was normal in 1/4 patients and FVC was reduced to 41% in 1/4 patients.<sup>e236</sup> CK levels were normal to 20-fold elevated. The characteristic muscle biopsy feature was many small vacuoles more prominent in type II fibers, although in isolated cases type I fibers had more vacuoles. On EM, the smallest vacuoles were focal dilations of the sarcoplasmic reticulum and coalesced to form larger vacuoles, often with degeneration of their muscle membranes.<sup>e234,e235</sup>

***LGMD2I/fukutin-related protein (FKRP).*** Three Class I studies,<sup>e57,e69,e238</sup> one Class II study,<sup>e239</sup> and 27 Class III studies<sup>e17,e52-e56,e144,e149,e197,e240-e257</sup> were reviewed. LGMD2I is a common cause of LGMD in white populations in northern Europe, Denmark,<sup>e69</sup> Italy,<sup>e17</sup> Germany,<sup>e52,e257</sup> Norway,<sup>e57</sup> and the United Kingdom,<sup>e245</sup> and has also been described in North America, Brazil,<sup>e238</sup> and in families of Tunisian and Bedouin descent. The mean age at onset was 12.7 years in one Class I study<sup>e57</sup> and 20.2 years in another Class I study.<sup>e238</sup> In Class III studies the age at onset ranged from 1.5–54 years, with means ranging from 9–23.2 years.<sup>e17,e52-e54,e149,e240,e242,e243,e245,e253,e257</sup> Weakness was symmetric and proximal, affecting the legs earlier and more severely than the arms, as reported in 2 Class I studies<sup>e69,e238</sup> and 11 Class III studies.<sup>e52-e54,e56,e149,e240,e242,e243,e245,e253,e257</sup> In the legs, hip flexion and hip adduction were particularly affected,<sup>e69,e149,e240</sup> whereas in the arms shoulder adduction<sup>e149,e240</sup> and elbow flexion<sup>e69,e149</sup> were especially affected. Facial weakness was reported in 3/18 in one Class III study<sup>e256</sup> but was not



reported in one Class I study and 3 Class III studies.<sup>e56,e69,e240,e257</sup> No dysarthria or dysphagia was reported, nor atrophy of any specific muscle groups. Scapular winging was noted in 3/20 patients,<sup>e53</sup> 6/11 patients,<sup>e240</sup> and 3/7 patients.<sup>e56</sup> Contractures did occur but were not a prominent feature; occasional ankle contractures were reported in 2/7,<sup>e56</sup> 2/16,<sup>e245</sup> and 2/27 homozygotes and in 5/11 compound heterozygotes (Class I).<sup>e69</sup> One Class III study reported contractures of the tibialis anterior (17/18), hips (3/18), knees (4/18), and elbows (3/18),<sup>e256</sup> whereas no contractures were observed in other series.<sup>e240,e242,e243,e257</sup> Calf hypertrophy was common.<sup>e52-</sup>  
<sup>e56,e69,e238,e242,e245,e246,e249,e256,e257</sup> Hypertrophy was also noted in some patients in the brachioradialis,<sup>e54,e245</sup> the thigh,<sup>e256</sup> and the tongue.<sup>e53-e55,e69,e240,e245,e246,e257</sup>  
Dilated cardiomyopathy was common clinically or by echocardiogram.<sup>e52,e53,e55,e69,e197,e239,e240,e245-e249,e252,e253,e255-e257</sup> One study using cardiac MRI disclosed myocardial fibrosis in 4/7.<sup>e197</sup> In this study, age, muscle strength, ability to ambulate, severity of dystrophic changes on muscle biopsy, and age at symptom onset did not correlate with cardiac involvement. Respiratory dysfunction was common, with a reduced FVC in a restrictive pattern observed in 2 Class I studies<sup>e57,e69</sup> and in 7 Class III studies.<sup>e17,e53,e55,e56,e240,e243,e245</sup> FVC was reduced 45%/62%/66%/82%/50% of the time,<sup>e53,e240,e243,e245,e253</sup> often moderately to severely; respiratory support in the form of noninvasive positive pressure ventilation or assisted ventilation was necessary in 20% to 25% of patients in the Class I studies<sup>e57,e69</sup> and in up to 45% of patients in the Class III studies.<sup>e53,e55,e57,e156,e240,e243,e245,e256</sup> Cognitive dysfunction was not mentioned in most studies, but was specifically noted to be absent in 2.<sup>e53,e242</sup> Formal cognitive testing was performed in 2 studies.<sup>e240,e253</sup> In one, 10/11 patients had normal verbal/written memory, and only 1/11 had a low IQ.<sup>e240</sup> In the second, mild impairment of executive function and visuospatial planning without a global reduction in IQ was common.<sup>e253</sup>

CK levels were almost always more than 10-fold elevated, as reported in 2 Class I studies<sup>e69,e238</sup> and 12 Class III studies.<sup>e17,e52-e55,e240,e242-e245,e251,e257</sup> Episodes of myoglobinuria were reported in 5/14 in one Class III study<sup>e250</sup> and in 7/26 in another.<sup>e253</sup> MRI studies of the legs revealed abnormal signal and fatty infiltration of the psoas, gluteus maximus, and thigh adductors, with relative preservation of the anterior thigh.<sup>e144,e149,e240</sup> The gracilis and sartorius muscles were involved later and were sometimes spared or even hypertrophied.<sup>e149</sup> MRI studies of the arms revealed abnormalities in the serratus, subscapularis, infraspinatus, and supraspinatus, with relative preservation of the triceps; the deltoids and biceps were either spared or involved later. Muscle biopsies were notable for dystrophic changes, including necrosis, evidence of degeneration and regeneration, variation in fiber size, internal nuclei, and fibrosis.<sup>e56,e69,e240,e245</sup> Reduced  $\alpha$ -dystroglycan immunoreactivity was observed.<sup>e54,e241,e244,e257</sup> Rimmed vacuoles, inclusions, and inflammation were absent.

***LGMD2J/Udd distal myopathy/hereditary myopathy with early respiratory failure (titin).*** Ten Class III studies were reviewed.<sup>e258-e267</sup> An additional article referenced in Udd<sup>e258</sup> was also reviewed for clinical details.<sup>e268</sup> There are 3 major clinical phenotypes of titinopathies: autosomal recessive LGMD2J, autosomal dominant distal myopathy, and autosomal dominant hereditary myopathy with early respiratory failure (HMERF).

***LGMD2J.*** LGMD2J has been reported mainly in Finnish and French populations.<sup>e258,e259,e264</sup> Onset of weakness was in the first 3 decades of life, but one Finnish patient was noted to have initial delayed motor milestones that subsequently stabilized, only to develop weakness around age 10 years.<sup>e264</sup> All patients had severe proximal muscle weakness and atrophy involving the

pelvifemoral and scapulohumeral muscles, with milder distal weakness (anterior tibial, gastrocnemius, forearm, and hand), and developed severe generalized weakness and wheelchair dependence over the subsequent 20 years. The face was spared, and scapular winging was described in only one patient. Muscle hypertrophy was not noted. One Finnish patient with onset in the early school years died at age 64 years from respiratory failure; no details were provided. At autopsy the heart was normal without signs of heart failure. One of the 7 patients initially described had atrial fibrillation, and another patient had “occasional cardiac arrhythmia.” Echocardiogram performed in 3/7 patients was normal. In contrast to this presentation, an early-onset recessive myopathy with severe cardiomyopathy characterized by delayed milestones and predominantly lower extremity proximal and distal weakness (but also involving proximal upper extremity, trunk, and face weakness and ptosis) has been described in Moroccan and Sudanese patients. In these 5 patients, pseudohypertrophy of the thighs and calves contrasted with atrophy of the upper limbs. Spinal rigidity and moderate joint contractures appeared in the first decade. The muscle disease was mild, but a progressive, severe dilated cardiomyopathy developed in all 5 patients, with rhythm disturbances. Sudden death occurred in 2 at 19.5 and 17.5 years.<sup>e267</sup> CK elevation was usually moderate (3–5 times normal); one patient with >10-fold elevation was reported. Muscle MRI was abnormal in all 22 patients in one study. Eight of the 22 patients had fatty replacement of leg muscles (anterior compartment only in 6, both anterior and posterior compartments in 2). Fourteen patients had both thigh and leg involvement. The hamstrings were uniformly involved: quadriceps in only 3 patients, gracilis in one patient. The lateral leg compartment was usually spared, being involved in only one patient at a late stage of the disease.<sup>e263</sup> Muscle biopsies revealed dystrophic features, and rimmed vacuoles were usually absent or rare.<sup>e258,e264,e268</sup>

*Udd distal myopathy.* Distal myopathy due to titin mutations has been described in Finnish, French, and Belgian populations.<sup>e259-e262,e264</sup> In contrast to the LGMD phenotype due to the same protein defect, the age at onset of distal myopathy is in the fifth to seventh decade of life. The muscle weakness predominated in the anterior tibial leg compartment in all patients, with mild weakness of the pelvifemoral and gastrocnemius muscles in a few patients (6/41 and 2/41). Atrophy of the anterior tibial muscles was noted in 26/41 and of the gastrocnemius in 1/12 patients.<sup>e259,e260</sup> The tibialis posterior and peroneus longus were also mildly weak in one patient.<sup>e262</sup> CK levels were normal or mildly elevated (30%–64%).<sup>e260,e261,e263</sup> One Belgian patient had CK levels >10 times normal.<sup>e262</sup> Cardiac involvement was absent.<sup>e261</sup> CT scan revealed fatty infiltration in the anterior tibial muscles in 7/9 patients and patchy involvement in the gastrocnemius and pelvic muscles in one patient each.<sup>e258</sup> In one Belgian patient, fatty degeneration of the tibialis anterior and extensor digitorum longus muscles, and to a lesser extent the gluteus medius and minimus muscles, was noted.<sup>e262</sup> Muscle biopsy revealed rimmed vacuoles in 28% of patients in the largest study.<sup>e260</sup>

*Hereditary myopathy with early respiratory failure.* HMERF recently has been reported to be caused by mutations in titin in Swedish<sup>e265</sup> and English<sup>e266</sup> families. The phenotype merges with that of LGMD2J and Udd distal myopathy. Like Udd, it is inherited in an autosomal dominant fashion and has an early predilection for the anterior compartment of the distal lower extremity leading to progressive foot drop. However, it tends to affect patients earlier in adulthood (range 18–71 years) and may affect the proximal muscles (legs greater than arms), as seen in LGMD2J.

The majority of patients have prominent calf hypertrophy. Ventilatory muscle weakness gradually develops over time; however, cardiomyopathy is not seen.

One report noted that the most commonly affected muscles on MRI were the semitendinosus (20 of 21 subjects), the peroneus longus (16/21), and the obturator externus (15/21).<sup>e266</sup> In the other series, MRI revealed fatty replacement mainly of the iliopsoas, rectus abdominis, obturatorius, and gluteus minimus muscles. Severely affected muscles in the thighs were the semitendinosus, gracilis, sartorius, vastus lateralis, intermedius, and medialis muscles, whereas the adductor longus muscles were relatively spared. In the lower legs, there was fatty replacement predominantly in the anterior and lateral compartments. Muscle histopathologic features included rimmed vacuoles, eosinophilic inclusions, desmin deposits, and extensive myofibrillar lesions with marked Z-disk alterations on EM resembling those described in MFM; thus, titin mutations of the HMERF phenotype should be added to the differential diagnosis of MFM.

***LGMD2K (protein-O-mannosyltransferase 1 or POMT1).*** One Class III study<sup>e59</sup> evaluated 3 patients with LGMD, ethnicity unspecified. Onset of disease was in infancy in 2 patients and at 3 years in one patient. Details of muscle involvement were not described. Muscle hypertrophy was noted in all 3 patients, but muscles involved were unspecified. Other phenotypes associated with *POMT1* mutations in this study included WWS (1), MEB/FCMD (1), and CMD-MR (3). CK levels were elevated >10 times. All patients had microcephaly and intellectual disability (mental retardation). Brain MRI showed minimal white matter changes in one patient and normal results in 2 patients. This study also included one patient with LGMD2K described by the authors previously; the studies were therefore reviewed together.<sup>e244</sup>

**LGMD2L (*anoctamin-5*).** Four Class III studies were reviewed.<sup>e61,e269-e271</sup> Earlier reports of these families were also reviewed for clinical details.<sup>e272,e273</sup> The disorder was initially reported in patients of French Canadian, Finnish, or Dutch descent, but subsequently in Australian, Spanish, Italian, German, and Afghan patients. Patients manifested with a limb-girdle pattern of weakness (LGMD2L) or with distal weakness resembling Miyoshi myopathy. The latter has been referred to as Miyoshi myopathy type III (MM3), but these phenotypes often overlap over time. Patients also presented for evaluation of hyperCKemia.<sup>e61,e269-e271</sup> One study included 7 patients with LGMD2L and 5 patients with distal myopathy.<sup>e269</sup> Another study reported long-term follow-up of 2 patients of Finnish descent with MM3 as reported in the first study.<sup>e270</sup> A third study found 25 patients with *ANO5* mutations out of a cohort of 101 patients with recessive LGMD, calf weakness, or hyperCKemia.<sup>e61</sup> The final study reported 4 patients: one with LGMD, one with distal myopathy, one with hyperCKemia, and one with weakness and atrophy of the quadriceps and medial calves.<sup>e271</sup> Age at onset ranged from 20–55 years (mean 34.4 years) in LGMD2L and 20–51 years (mean 36 years) in patients presenting with distal myopathy. Five of 7 patients (71%) with LGMD2L had weakness of the pelvic and scapular girdles. One patient also had mild weakness of the calf muscles and another of the tibialis anterior. One patient had atrophy and weakness of the right biceps brachii and right posterior thigh atrophy on examination initially, despite involvement of lower extremity muscles on MRI, and developed asymmetric hamstring weakness after 2 years.<sup>e61</sup> Asymmetric atrophy of the biceps and quadriceps was noted in many patients across reports. Patients with distal myopathy had early calf weakness with difficulty in toe walking; the calf muscles were noted to be atrophic, often asymmetrically. However, some patients had calf hypertrophy early in the course before atrophy ensued. Atrophy or weakness of

the quadriceps was noted in some patients with LGMD and some patients with distal myopathy.<sup>e269-e271</sup> Atrophy was also appreciated later in the course in the biceps and pectorals.<sup>e270</sup> CK levels were elevated 8- to >20-fold. Five patients across the studies had asymptomatic hyperCKemia noted in the fourth decade or later, although one had calf hypertrophy. Echocardiography, ECG, and Holter monitoring were normal in all the patients who were tested across studies.<sup>e61,e269-e271</sup> No pulmonary abnormalities were noted in one study.<sup>e61</sup> In 2 patients, muscle MRI showed atrophy and fat replacement of the long head of the biceps brachii. Muscles most involved in the legs were the medial gastrocnemius, adductor magnus, hamstrings, tensor fasciae latae, and to a lesser extent the quadriceps, often asymmetrically.<sup>e61,e273</sup> In one of the 2 patients with distal myopathy who were followed long-term, initial muscle MRI at disease duration of 10 years showed fibrofatty degeneration in the gastrocnemius. Subsequent studies revealed similar changes in the soleus and biceps brachii. The other patient with distal myopathy also had asymmetric changes in the adductor magnus, vastus lateralis and intermedius, and tensor fasciae latae.<sup>e270</sup> Muscle biopsies revealed myopathic/dystrophic changes. EM revealed multifocal disruption of the sarcolemmal membrane.<sup>e61,e270</sup>

***LGMD2M (fukutin).*** Three Class III studies were reviewed.<sup>e59,e244,e274</sup> There were only 5 patients from 3 families reported across these studies. The disorder was described in one Israeli family in one study and in the child of Jewish and East Indian parents in another study. The ethnicities in the other cases were unspecified.<sup>e274</sup> The onset of illness was from 4 months to 4 years of age. The phenotype was described as LGMD without intellectual disability (mental retardation) in 2 studies, with lower extremities more affected in 2/3 cases and upper extremities more affected in 1/3 cases. Muscle hypertrophy was described in 4/5 cases in one study, but the muscle group was

not specified.<sup>e59</sup> In another study, 2/3 patients had lateral calf hypertrophy.<sup>e274</sup> Unspecified contractures were reported in 2/5 patients.<sup>e59</sup> Cognitive function as defined by IQ was normal in all 5 patients, and brain MRI showed mild hydrocephalus in one patient and normal results in 2 patients. Increased weakness with a febrile illness was reported in 2 patients. All patients had CK levels more than 10 times normal. The muscle biopsy was significant for the presence of inflammation with macrophages, CD8+ lymphocytes, and major histocompatibility complex class I antigen upregulation in 2 cases.<sup>e59,e274</sup>

***LGMD2N (protein-O-mannosyltransferase 2 or POMT2).*** Two Class III studies<sup>e59,e244</sup> and one Class IV study<sup>e275</sup> were available. The Class IV study was retained because of the rarity of the disorder. One Class III study was excluded because it reported only patients with MEB and CMD, which are not addressed in this guideline.<sup>e244</sup> The other 2 studies describe only one patient each with LGMD2N.<sup>e59,e275</sup> One patient presented with developmental delay at 18 months and had an LGMD phenotype with learning difficulties at age 20 years.<sup>e59</sup> Hypertrophy was mentioned but not described further. Cardiac evaluation revealed right bundle branch block. The second patient was found to have elevated CK levels incidentally. She had calf hypertrophy. At age 5 years, scapular winging, mild proximal lower extremity weakness, and lordosis were evident. Intellectual development and brain MRI were normal. CK levels were >10 times normal. Cardiac evaluation, not described further, was normal. Muscle biopsy revealed dystrophic changes with inflammatory infiltration of macrophages and lymphocytes.

***LGMD2O (protein O-linked mannose beta1,2-N-acetylglucosaminyltransferase or POMGNT1).*** Two Class III studies<sup>e59,e244</sup> and one Class IV study<sup>e276</sup> were reviewed. Each study



described only one patient, but all studies were retained because of the rarity of the disorder.<sup>e59,e244,e276</sup> Age at onset was 12 years in one case<sup>e59</sup> and 21 in another.<sup>e276</sup> All 3 patients had a limb-girdle pattern of weakness, with neck, hip girdle, and shoulder abductors particularly affected in one.<sup>e276</sup> Hamstrings and deltoids were atrophic; calves and quadriceps were hypertrophic.<sup>e59,e276</sup> Contractures were absent in one patient and were not described in the others.<sup>e59</sup> Cognitive function was normal in all 3 patients. CK levels were elevated >10 times above normal. Cardiac and respiratory involvement were not described. Muscle biopsy in one patient revealed basophilic fibers, some of which were granular, with vacuoles.<sup>e276</sup> In another study, the patient with the more severe CMD phenotype was noted to have a severe reduction in the glycosylation of  $\alpha$ -dystroglycan compared with the patient with the milder LGMD phenotype.<sup>e244</sup>

***LGMD2P ( $\alpha$ -dystroglycan).*** One Class IV study<sup>e277</sup> reported a 16-year-old Turkish female with LGMD. The clinical features were reported in an earlier study.<sup>e278</sup> The patient was born of consanguineous parentage. Age at onset was 3 years with unsteady gait and difficulty climbing stairs. Waddling gait and Gower maneuver were seen at age 10, with microcephaly, increased lumbar lordosis, mild calf hypertrophy, and ankle contractures. Facial weakness or muscle atrophy was not noted. Proximal muscle weakness was observed. Intellectual developmental delay was noted, and IQ at age 16 was 50. CK levels were elevated >10 times at 4,133 U/L and cranial MRI was normal. Muscle biopsy revealed a reduction of  $\alpha$ -dystroglycan on immunohistochemistry. The initial description of the patient also reported 8 patients from 7 families with reduced  $\alpha$ -dystroglycan expression on muscle biopsy, all characterized by LGMD

with onset in the first decade, severe cognitive impairment, and normal brain MRI, but genetic confirmation was not available.<sup>e278</sup>

***LGMD2Q (muscular dystrophy associated with epidermolysis bullosa [plectin-1]).*** Thirty articles were reviewed. Most of these were case reports or small case series of up to 4 patients and were included in this guideline because of the rarity of the disorder.<sup>e279-e308</sup> This has recently been designated LGMD2Q and is also considered a form of congenital myasthenia.<sup>e279,e282,e293,e303,e306</sup> The disorder has been described in several ethnicities, including Dutch, Australian, Japanese, Hispanic, Italian, British, German, and Austrian patients. The characteristic feature was epidermolysis bullosa, in which patients develop blistering of the skin and mucous membranes, usually noted at birth or shortly after. Nail dystrophy was also present. Later in life a progressive muscular dystrophy develops. The onset of dystrophy varied from infancy to as late as the fourth decade, presenting with either hypotonia in the neonatal period, developmental delay, or slowly progressive weakness in late childhood or adulthood. The muscle weakness was described in only a few cases and was in a limb-girdle distribution, with the lower extremity involved more severely.<sup>e292,e302</sup> Ptosis and ophthalmoplegia as well as facial weakness were described in a few cases.<sup>e283,e292</sup> Dental caries, scarring alopecia, urethral strictures, pyloric atresia, esophageal strictures, respiratory distress, and, rarely, cardiomyopathy were associated features. The frequency of these features was difficult to determine given descriptions of individual cases. CK levels were elevated to varying degrees from <10 times to >10 times normal. Muscle biopsy showed myofiber nuclei in subsarcolemmal rows or clusters. Type I fiber predominance was seen in a few cases. Oxidative stains showed irregular distribution of activity. Myofibrillar disarray and Z-disk streaming were seen on EM. Immunohistochemistry showed

loss of sarcolemmal and trace sarcoplasmic activity of the antibody to the rid domain of plectin-1 in type I fibers, whereas type II fibers retained activity. Antibody to the last 50 C-terminal residues of plectin was absent in the sarcoplasm and showed only slight immunoreactivity in both type I and type II fibers in one study.<sup>e293</sup>

**BMD.** We reviewed 3 Class I studies<sup>e309-e311</sup> and 54 Class III studies.<sup>e65,e66,e68,e156,e208,e312-e360</sup> Bushby et al.<sup>e311</sup> is reviewed along with Bushby and Gardner-Medwin<sup>e309</sup> and Bushby et al.<sup>e310</sup> because the former is an earlier report of the same cohort. In a 2-part Class I natural history study of 67 patients with BMD,<sup>e309,e310</sup> the age at onset ranged from 10 months to 38 years, with a mean of 11.2 years. Four patients (6%) with genetic confirmation were asymptomatic. Six of 67 (18%) used a wheelchair (mean age of wheelchair dependency was 37.6 years). Those patients with mutations involving exons 45–47 had prolonged ambulation. Myalgias occurred in 27%, calf pain in 81%, and myoglobinuria in 2%. IQ testing was done in only 6 patients and was noted to be in the low-average range, with verbal performance score discrepancy. Most patients (87.9%) attended a mainstream school, but 6.8% attended a school for those with a learning disability and 3.4% a school for those with a physical disability. ECG was abnormal in 14/34 patients tested. The abnormalities included incomplete right bundle branch block (9 patients), Q waves in V4-6 and aVF (5 patients), left ventricular hypertrophy (4 patients), tall R waves in the right chest leads (3 patients), and nonspecific T-wave abnormalities (3 patients). FVC, measured in 41 patients, was generally reduced compared with the expected change for FVC in a comparable normal population. Serum CK levels ranged from 630 to 35,000 U/L, with a mean of approximately 5,200 U/L (>10 times normal).

The 54 Class III studies are summarized here.<sup>e65,e66,e68,e156,e208,e312-e360</sup> Symptom onset occurred from early childhood to late adulthood. The pattern of weakness, when present, was proximal-greater-than-distal, with legs more affected than arms. Some patients manifested with only myalgias or episodic myoglobinuria.<sup>e315,e331,e357,e358</sup> Most patients had calf hypertrophy; contractures were late and first appreciated at the ankles. Variability in the severity of the clinical phenotype was seen even within families harboring the same mutation.<sup>e330</sup>

A mild decrease in IQ on average and learning problems were seen in some patients. In a study of neuropsychological testing of 28 patients, 5 had an IQ less than 70 and 13 had an IQ between 70 and 85. The mean IQ was 87.8 (SD 14.8).<sup>e318</sup> Another study reported normal IQ (mean 95.6) in 23 patients. However, in 17 males who were tested, a high prevalence of learning abnormalities was noted (reading problems in 21%, spelling in 32%, arithmetic in 26%).<sup>e352</sup> A third study of 28 patients with BMD revealed borderline MR in only one patient and a mean IQ of 85.9.<sup>e335</sup> Dilated cardiomyopathy with reduced EF occurred in 4% to more than 70%, depending on the duration of illness.<sup>e66,e156,e312,e315,e316,e319,e321,e322,e324,e328-e330,e332,e334,e337,e340,e341,e345,e347,e359,e360</sup> In the largest series (98 patients), more than 40% developed a cardiomyopathy.<sup>e315</sup> In addition, nonspecific ECG abnormalities were seen in the majority of patients.<sup>e312,e313,e321,e328,e333,e340,e341,e346-e348,e356,e357</sup> There was a wide range of CK levels, from slightly to markedly elevated. Muscle biopsies usually revealed reduced immunostaining for dystrophin, but Western blot was more sensitive and demonstrated reduced size or amount of dystrophin.<sup>e66,e315-e317,e320,e321,e331</sup> Abnormal immunostaining to sarcoglycans has also been observed.<sup>e343,e347</sup>

***Females manifesting with dystrophinopathy.*** Sixteen Class III studies were reviewed.<sup>e65,e328,e356,e357,e361-e372</sup> Hoogerwaard et al.<sup>e366</sup> and Hoogerwaard et al.<sup>e367</sup> describe the same cohort of patients and are reviewed together. Symptom onset was reported to be between ages 2 and 48 years.<sup>e357,e361-e363,e366,e368,e370,e372</sup> Patients manifested most frequently with muscle pains with or without a limb-girdle pattern of weakness; 30%–75% had noticeable calf hypertrophy. Asymmetric weakness was noted in 3/15 patients in one study.<sup>e370</sup> In one study, 1 of 5 patients had tight heel cords. Weakness could be severe as in DMD or mild like BMD.<sup>e65,e356,e358,e361,e362,e364,e368,e371,e372</sup> In a 10-year study of 197 carriers (152 DMD, 45 BMD), 9 DMD (5.9%) and 3 BMD (6.6%) carriers presented with mild calf pseudohypertrophy and 4 DMD carriers (2.6%) had marked proximal wasting and weakness.<sup>e369</sup> Normal cardiac status was observed in 15 (45.5%) of the 33 carriers aged between 5 and 15 years but in only 16 (9.8%) of the 164 carriers older than 15 years ( $p < 0.001$ ). On the other hand, clinically evident myocardial damage was found in 5 (15.1%) of the 33 carriers aged between 5 and 15 years but in 73 (44.5%) of the 164 carriers older than 15 years ( $p < 0.001$ ). The authors concluded that cardiac involvement in carriers of DMD/BMD is more frequent with increasing age.<sup>e369</sup> In another study, 30 of 264 carriers (11%) to 5 of 15 carriers (33%) of DMD/BMD mutation (not necessarily manifesting carriers) had dilated cardiomyopathy on echocardiography; 50/164 (30.5%) had evidence of hypertrophic cardiomyopathy and 7/186 (4%) had arrhythmia of some type on ECG.<sup>e328,e365,e369,e370</sup> CK levels were only slightly to markedly elevated to >10 times normal.<sup>e65,e356,e361-e364,e368,e371,e372</sup> Immunohistochemistry on muscle biopsies usually revealed a mosaic pattern for dystrophin.<sup>e356,e357,e362,e363,e371,e372</sup> A few studies reported preferential inactivation of the putative X chromosome carrying the normal dystrophin allele in most, but not all, affected females.<sup>e362,e363,e372</sup>

***X-linked Emery-Dreifuss muscular dystrophy/EDMD-X1 (emerin).*** Twelve Class III studies were reviewed and are summarized here.<sup>e81,e373-e383</sup> There was a wide range in age at onset or detection, varying from 14 months to 62 years across the various studies. European, Japanese, and North American kindreds were described. Gradually progressive weakness and atrophy were most typically described in a humeroperoneal pattern, although pelvifemoral distribution of weakness was also described in some families and scapular winging was not infrequent.<sup>e81,e376,e378</sup> Most patients remained ambulatory into late adulthood.<sup>e81,e378</sup> Rigidity of the spine with an exaggerated lumbar lordosis and contractures at the elbows and Achilles tendon were characteristic features, but inter- and intrafamilial phenotypic variation was frequent; contractures occurred in some patients in the absence of muscle weakness.<sup>e376,e377,e380,e383</sup> Cardiac arrhythmias were an important and prominent clinical feature. Conduction disturbances were common, particularly sinus node dysfunction with varying degrees of atrioventricular block progressing to atrial standstill, or paralysis.<sup>e81,e373,e375,e376,e378,e381,e383</sup> Notably, conduction abnormalities did not correlate with the severity of skeletal muscle involvement and were described in several patients without any associated myopathic features, including symptomatic nonsustained ventricular tachycardia in 2 patients.<sup>e381</sup> A large percentage of patients among studies required permanent pacemaker implantation: 10/12,<sup>e373</sup> 3/3,<sup>e375</sup> 15/23,<sup>e81</sup> 3/5,<sup>e377</sup> 4/4,<sup>e381</sup> and 7/7,<sup>e383</sup> for a combined reported incidence of 42/54 (77.8%). Cardiac conduction abnormalities presented at an early age; pacemaker implantation occurred at a mean age between 20 and 35 years in various studies (range 15–42 years).<sup>e81,e373,e375-e377</sup> Female carriers were also found to have a high incidence of cardiac conduction abnormalities, increasing with increasing age: 6/34 (18%) overall, 1/29 below the age of 59 years, increasing to 5/5 over the age of 60 years.<sup>e373</sup> Pacemaker requirement was reported in 2/34 (6%),<sup>e373</sup> 2/9 (22%),<sup>e383</sup> and 3/5 (60%)<sup>e81</sup>

female carriers. Thromboembolic stroke was reported in 4 patients.<sup>e81,e383</sup> Sudden cardiac death was reported in 2 studies, including 5/23 subjects (22%) in one long-term follow-up study<sup>e373</sup> and 3/33 subjects (9%) in 2 families,<sup>e383</sup> occurring at mean ages of 47 years<sup>e373</sup> and 34.7 years,<sup>e383</sup> respectively (range 27–67 years).

In contrast to the severe conduction abnormalities, CHF was not a clinical feature of emerinopathy, and echocardiography was often found to be normal.<sup>e81,e375,e376</sup> However, abnormalities were not infrequent; characteristically, atrial abnormalities, particularly of the right atrium, predominated.<sup>e377,e378,e383</sup> In a 5-year longitudinal study,<sup>e377</sup> 1/5 patients showed right atrial enlargement (RAE) at the outset whereas 4/5 were normal; over the follow-up period, 2 more patients developed RAE. All 3 patients with RAE progressed to biatrial enlargement with early left ventricular enlargement by 5 years; only one patient had LVEF reduced to 45%. Another study revealed RAE in 7/7 (100%) and biatrial enlargement in 2/7 (29%) but no cardiomyopathy.<sup>e383</sup> In one series examining left ventricular function by echocardiography, 6/23 patients (26%) had LVEF <50% and 3 of these had severe LVEF compromise (<35%); 2 were asymptomatic.<sup>e378</sup>

CK levels ranged from normal to mildly elevated (<3 times normal) and were noted to peak during adolescence and then decline in adulthood. In a study of 33 obligate female carriers, CK levels were normal in 100%.<sup>e81,e374-e376,e379</sup> Muscle imaging revealed variable involvement of posterior leg muscles, most severely affecting semimembranosus muscles in the thigh and soleus and medial gastrocnemius in 5/5 patients.<sup>e381</sup> Immunohistochemistry on muscle biopsies revealed absent or markedly reduced emerin staining.<sup>e81,e377,e379,e382,e383</sup> One study found absence of emerin staining on immunohistochemistry of buccal epithelial cells in 3/3 affected males and reduced amounts of nuclear staining in female carriers.<sup>e381</sup> Immunocytochemistry on skin biopsies

demonstrated absence of emerin staining, whereas immunoblotting of peripheral blood cells showed absence or reduced intensity of the emerin band.<sup>e382</sup> Muscle biopsies in 2 cases from one family showed rimmed vacuoles and tubulofilamentous inclusions typical of inclusion body myopathy.<sup>e379</sup>

***EDMD-X2/scapuloperoneal myopathy (four-and-one-half LIM1 protein or FHL1).***

Eleven Class III studies were reviewed.<sup>e384-e394</sup> Pedigrees included German, Italian-American, Austrian, Croatian, British, Japanese, and northern European. The age at onset showed a wide range, from infancy<sup>e389</sup> to the eighth decade,<sup>e392</sup> but most commonly occurred between childhood and middle age.<sup>e387-e391,e393</sup> The clinical phenotypes included limb-girdle weakness,<sup>e387,e388,e390,e393</sup> anterior tibial weakness with early foot drop,<sup>e385,e392</sup> scapuloperoneal weakness,<sup>e385,e388,e390</sup> and rigid spine syndrome.<sup>e384,e386,e390,e394</sup> Prominent biceps atrophy was noted in 2 studies.<sup>e391,e393</sup> Athletic hypertrophic appearance was seen in some cohorts, especially early in the course of the disease.<sup>e384,e388,e390</sup> Scapular winging was noted to be common<sup>e385,e388</sup> but more often was not reported. Dysphagia and dysarthria were rare.<sup>e386,e387,e392</sup> Extremity contractures<sup>e384,e386-e388</sup> and neck contractures were common.<sup>e384,e386,e388,e390,e392,e393</sup> Some patients had a cardiomyopathy.<sup>e384,e386,e387,e390</sup> Severe respiratory failure was seen in many patients,<sup>e386,e388,e390</sup> particularly early-onset patients.<sup>e387</sup> CK levels were normal or elevated to <10 times normal.<sup>e384,e387,e388,e390,e392,e393</sup> Muscle biopsies frequently showed reducing bodies and cytoplasmic bodies.<sup>e384,e386,e387,e392,e394</sup> Two reports found cytoplasmic bodies without reducing bodies.<sup>e384,e388</sup> *FHL1* immunostaining was used in several studies and noted to be positive for reducing bodies.<sup>e384,e387,e390-e392</sup>



***Myofibrillar myopathies.*** The term myofibrillar myopathies (MFMs) is used to describe a group of muscular dystrophies that share specific, common morphologic features on muscle biopsy.<sup>e395,e396</sup> On light microscopy these abnormalities are best appreciated on the modified Gomori trichrome stains, in which the abnormal fibers harbor an admixture of amorphous, granular, or hyaline deposits that vary in shape and size and are dark blue or blue red in color. Many abnormal fiber regions, especially the hyaline structures, are devoid of or have diminished oxidative enzyme activity. Some hyaline structures are intensely congophilic. Some muscle fibers harbor small rimmed vacuoles. EM shows that disintegration of the myofibrils begins at the Z-disk, followed by accumulation of degraded filamentous material in various patterns, aggregation of membranous organelles and glycogen in spaces vacated by myofibrils, and degradation of dislocated membranous organelles in autophagic vacuoles. Immunostaining reveals ectopic accumulation of multiple proteins, including myotilin,  $\alpha$ B-crystallin, desmin, dystrophin, sarcoglycans, caveolin, neural cell adhesion molecule, plectin, gelsolin, ubiquitin, filamin C, Bag3, and others. One study reported differences between the distinct MFM subgroups: the consistent presence of “rubbed-out” fibers in desminopathies and  $\alpha$ B-crystallinopathies, an elevated frequency of vacuoles in ZASPopathies and myotilinopathies, and the presence of a few necrotic fibers in myotilinopathy patients.<sup>e397</sup>

In a separate study, the same group of authors reported that EM findings in desminopathies and  $\alpha$ B-crystallinopathies were very similar and consisted of electron-dense granulofilamentous accumulations and sandwich formations; they differed in the obvious presence of early apoptotic nuclear changes in  $\alpha$ B-crystallinopathies.<sup>e398</sup> ZASPopathies were characterized by filamentous bundles (labeled with the myotilin antibody on immune-EM) and floccular accumulations of thin filamentous material. Tubulofilamentous inclusions in sarcoplasm and myonuclei in combination

with filamentous bundles were characteristic for myotilinopathies. Rather than reiterating the hallmarks above in each of the subsequent MFM subtypes, we note that each of these disorders shows the characteristic MFM features on biopsy.

*Myotilin (LGMD1A)*. Nine Class III studies were reviewed.<sup>e9,e399-e406</sup> The age at onset was 18–79 years with limb-girdle or distal limb weakness. Asymmetric muscle weakness and atrophy were frequently noted across studies. Scapular winging was not reported. Dysarthria was found in 4/16 affected individuals of a single kinship who were assigned as having LGMD1A<sup>e402</sup> and in the most-affected family members of another large kinship<sup>e401</sup>; another patient had hypernasal speech.<sup>e403</sup> Ten of 16 in the initial report<sup>e407</sup> (cross-referenced in Hauser et al.<sup>e402</sup>), 1/5,<sup>e9</sup> and 4/13<sup>e403</sup> patients had tight heel cords. Cardiac abnormalities were seen in 3/5,<sup>e9</sup> 2/13,<sup>e403</sup> 1/24,<sup>e406</sup> and 1/12<sup>e400</sup> patients. Respiratory failure was present in 3/13,<sup>e403</sup> 3/24,<sup>e406</sup> and several affected family members of a large kinship.<sup>e401</sup>

Serum CK levels were normal to <10-fold elevated. Muscle-imaging studies revealed involvement of the medial gastrocnemius, soleus, hip adductors, and biceps femoris with fatty/fibrous replacement and edema; the semitendinosus was relatively spared.<sup>e399,e400,e403,e405,e406</sup> Muscle biopsy showed features of MFM. Myofiber necrosis and inflammatory infiltrates were also seen occasionally.<sup>e9,e399,e403,e406</sup>

*Desmin (LGMD1E)*. There were 17 Class III studies.<sup>e400,e405,e406,e408-e421</sup> The myopathy was usually inherited in an autosomal dominant fashion, although sporadic cases were reported. Age at onset ranged from the first to the sixth decade of life. The pattern of muscle weakness was most often distal-greater-than-proximal<sup>e409,e411-e413,e415,e417,e418</sup> with the earliest manifestation

being progressive foot drop, but proximal-greater-than-distal weakness,<sup>e413,e420</sup> proximal and distal weakness,<sup>e408-e410,e413,e415-e417</sup> and a scapuloperoneal distribution<sup>e413</sup> were also reported. Face and bulbar muscles were affected in some with dysphagia or dysarthria.<sup>e408,e412,e413,e415-e418,e420</sup> Ventilatory muscle weakness was also common.<sup>e411,e413,e415,e417,e418</sup> Cardiac involvement was common (40%–100%) across all series, with onset often preceding muscle weakness.<sup>e400,e406,e408-e410,e412-e418,e420</sup> Onset of cardiac symptoms ranged from the first to the seventh decade of life. The most common cardiac manifestation was cardiac arrhythmia, including atrioventricular conduction block, atrial fibrillation, other tachyarrhythmias, and cardiac conduction defects, and some patients required pacemaker or implantable cardioverter defibrillator implantation. Dilated cardiomyopathy was more frequent than hypertrophic or restrictive cardiomyopathy. In a study of 21 members of a Swedish family, arrhythmogenic right ventricular cardiomyopathy was described in 3, and the authors suggested that the presence of a right ventricular cardiomyopathy (right ventricular dysfunction and tachyarrhythmias of right ventricular origin) was a clue to this disorder.<sup>e421</sup> Sudden death was reported in 3/18 patients, and 2/18 patients underwent cardiac transplantation in one series.<sup>e406</sup>

Serum CK levels were normal or only moderately elevated (up to 5 times normal) in the majority of patients.<sup>e409-e412,e416,e418</sup> Two studies focused on CT/MRI of skeletal muscles.<sup>e400,e405</sup> One study evaluated 19 patients and revealed gluteus maximus greater than gluteus medius or gluteus minimus involvement.<sup>e400</sup> In the thighs, the semitendinosus, sartorius, and gracilis were affected earlier than the adductor magnus, biceps femoris, or semimembranosus. The quadriceps muscles were relatively spared. In the distal legs, the peroneal muscles were affected more than the tibialis anterior, which was affected more than the posterior compartment. The other study evaluated 4 patients<sup>e410</sup> and reported that the iliopsoas, sartorius, gracilis, and semitendinosus

were affected in 3 of 4 patients, whereas the biceps femoris was involved in 2 patients and the semimembranosus in one. In the distal legs, the peroneal, tibialis anterior, medial gastrocnemius, and soleus were involved in 3 of 4 patients. Two patients had involvement of the paraspinal muscles and 2 of the shoulder girdle, whereas none had involvement of the humeral muscles in the arms. Another CT study of 4 patients showed the earliest abnormalities in the semitendinosus and sartorius, and later abnormalities in the gracilis muscles at the mid-thigh level and in the peroneal group followed by the anterior tibialis and posterior group at the mid-calf level.<sup>e417</sup> In the later stages of the illness all muscles except for the soleus were replaced by fatty tissue.

*$\alpha$ B-Crystallin.* Four Class III studies presenting a total of 9 patients were reviewed.<sup>e400,e422-e424</sup> The age at onset ranged from the 30s to the late 60s. Two patients presented with distal lower limb weakness with asymmetric muscle atrophy; one patient presented with diaphragmatic weakness followed by leg weakness and dysphagia.<sup>e422,e423</sup> Five patients from the same family had dysphagia and dysphonia, and 4 of them had cataracts.<sup>e424</sup> Scapular winging, dysarthria, or contractures were not described. Three patients had cardiomyopathy. Serum CK levels were normal to <10-fold elevated. Muscle-imaging studies showed involvement of gluteus maximus, sartorius, semitendinosus, vastus intermedius, medialis, lateralis, rectus femoris, tensor fasciae latae, adductor magnus, gracilis, and peroneal muscles.

*Z-band alternatively spliced PDZ motif-containing protein (ZASP) (Markesbery-Griggs distal myopathy).* Four Class III studies were reviewed.<sup>e72,e400,e406,e425</sup> The age at onset was 27 to 73 years. Patients presented with limb-girdle or distal lower limb weakness. In one study, all 10 patients from a single family had distal leg weakness at onset, followed by atrophy and weakness

of the hand muscles and wrist extensors.<sup>e425</sup> In another study of 3 patients, one had distal weakness and 2 had distal-greater-than-proximal weakness.<sup>e400</sup> Likewise, a third study had 5/11 patients with distal-greater-than-proximal weakness; only distal weakness occurred in one patient, only proximal weakness in 2 patients, and both proximal and distal weakness in 3 patients.<sup>e72</sup> One report of 7 patients<sup>e406</sup> also revealed distal-predominant weakness at onset that spread to involve distal and proximal muscles as the disease progressed. Scapular winging, dysphagia, or dysarthria was not noted. Ankle contracture was observed in one of 10 patients (10%) in one study.<sup>e425</sup> Cardiomyopathy was reported in 3 of 11 patients.<sup>e72</sup> Serum CK levels were normal to <10-fold elevated. Muscle MRI showed early involvement of posterior calf muscles, and the soleus muscle was the most affected. In the pelvis, the gluteus minimus was most affected in 3/3 patients. At the thigh level, the posterior compartment (biceps femoris and semimembranosus) was mostly involved, whereas the adductor magnus and gracilis were relatively spared. In the lower legs, one patient presented only with alterations in the soleus and medial gastrocnemius muscle at disease onset; in another case the soleus was most affected, and in the third case all lower leg muscles were involved.<sup>e400</sup> Muscle MRI performed in 2 patients in another study showed considerable involvement of posterior calf muscles.<sup>e425</sup> In another study, the adductor magnus, semimembranosus, vastus medialis, biceps femoris, soleus, and gastrocnemius were most frequently involved.<sup>e406</sup> Five of 11 patients had clinical or biopsy features of an associated neuropathy.<sup>e72</sup>

*BCL2-associated athanogene 3 (BAG3).* Two Class III studies describing 7 patients were reviewed.<sup>e73,e426</sup> One study<sup>e73</sup> reported 2 patients (one age 15 years and one age 11 years) presenting with a history of toe walking, the former since early childhood and the latter since he

was a toddler. The third patient presented at age 13 with scoliosis, rigid spine, and easy fatigability. The distribution of weakness was axial and moderately severe, with distal-greater-than-proximal weakness in one patient, moderate proximal weakness in one patient, and severe diffuse weakness in the third patient. One patient had scapular winging. Another patient had hypernasal speech. One patient had knee and ankle contractures. Two patients had restrictive cardiomyopathy, and one had mitral regurgitation. All 3 patients had respiratory involvement. CK levels were 3- to 15-fold elevated. Another study<sup>e426</sup> reported 4 patients from 3 families with weakness starting at ages 5 to 12 years. Two had predominantly proximal muscle weakness, restrictive/hypertrophic cardiomyopathy, and respiratory insufficiency; one developed bilateral pes cavus, neck and distal leg weakness, and restrictive cardiomyopathy with secondary enlargement of both atria, and the other developed restrictive cardiomyopathy, had a heart transplant at age 13 years, and became ventilator dependent. At age 15, he was noted to have predominantly proximal and respiratory muscle weakness.

*Filamin C (Williams distal myopathy).* Seven Class III studies were reviewed.<sup>e400,e427-e432</sup> Fischer et al.<sup>e400</sup> described muscle MRI findings of some of the patients previously reported in Kley et al.,<sup>e428</sup> so these 2 studies are reviewed together. Mean age at onset of weakness was early- to mid-40s. The patients presented with a limb-girdle pattern of proximal muscle weakness and atrophy with lower limb predominance; 6 of 31 patients had scapular winging. No dysphagia, dysarthria, hoarse voice, or contractures were noted. In a study of 13 patients from 3 related families, all patients presented with distal upper limb weakness with lower limb involvement upon disease progression.<sup>e431</sup> There was late-onset involvement of respiratory muscles in 14/31 patients, but no details were provided. Cardiac involvement was seen in approximately one-third,

including atrial flutter, right bundle branch block, decreased EF, and nonspecific cardiomyopathy. CK elevations were mild (<10-fold). Muscle MRI showed significant sparing of sartorius, gracilis, superficial parts of the quadriceps femoris, and the lateral gastrocnemius. There was involvement of gluteal muscles, semimembranosus, adductor magnus, biceps femoris, and vastus intermedius and medialis. The soleus and medial gastrocnemius were disproportionately involved compared with the lateral gastrocnemius and peroneal muscles. In one study, MRI of a single patient showed marked triceps surae with involvement of other lower leg muscles, with the exception of the posterior tibial muscle.<sup>e431</sup>

In a study of a Chinese family with 10 affected members over 4 generations, proximal muscle weakness and atrophy of the lower limbs were noted at the onset; as the disease progressed, all limbs were involved.<sup>e432</sup> The index patient had right bundle branch block and atrial and ventricular premature beats.

In a Class III study originally categorized as the Williams distal myopathy and subsequently confirmed to be due to filamin C mutations,<sup>e429,e430</sup> 12 affected members of a single Australian kindred were described with onset of distal upper and lower extremity weakness in early adulthood. Two additional family members were possibly affected. Age at onset varied considerably, but all cases reported onset by the fourth decade of life, and in many cases much younger: 5/27 reported onset in their teens and 4/27 reported onset around age 30 years. The characteristic pattern included early involvement of the distal anterior upper limb (selectively involving forearm pronators and finger flexors) and posterior leg (ankle plantar flexor) muscles, with sparing of the tibialis anterior, even in advanced disease. Muscle pain was a prominent feature. All patients remained ambulatory. None had evidence of cardiac or respiratory muscle involvement. Serum CK levels were either normal (5/8) or mildly elevated (<3 times normal in

3/8 patients). MRI showed widespread involvement of the posterior and lateral leg compartments in 4/7 patients (57%) and was normal in 3/7 patients (43%). In a similarly affected Italian family, the weakness started distally in the hand muscles with hand muscle atrophy and slowly progressed to involve the proximal muscles. Two of the 3 patients had cardiomyopathy.<sup>e430</sup> Muscle biopsies showed features of MFM except for patients in Duff et al.<sup>e430</sup> and Guergueltcheva et al.,<sup>e431</sup> whose biopsies showed nonspecific myopathic changes.

*Titin.* This is described under the section on LGMD2J/Udd distal myopathy/HMERF.

***Hereditary inclusion body myopathies.*** *Autosomal recessive hIBM/Nonaka distal myopathy (GNE).* Eleven Class III studies were reviewed.<sup>e433-e443</sup> In addition, another report (Sadeh et al.<sup>e444</sup>) before confirmation by genetic testing was also reviewed in conjunction with Mitrani-Rosenbaum et al.<sup>e434</sup> Autosomal recessive hIBM (AR-hIBM) and Nonaka distal myopathy are the same disorder caused by mutations in the gene encoding UDP-N-acetylglucosamine-2-epimerase/N-acetylmannosamine kinase (*GNE*). AR-hIBM was initially described in Iranian Jews and other Middle Eastern Karaites and Arab Muslims of Palestinian and Bedouin origin, whereas Nonaka distal myopathy was reported in Japanese, Korean, and Chinese families.<sup>e436-e439</sup> The age at onset ranged between the late teens and early 40s.<sup>e434,e436,e441</sup> The characteristic pattern of muscle involvement was early involvement of the anterior tibial muscles leading to progressive foot drop. Over time, proximal legs could be involved, but there was relative sparing of the quadriceps in comparison to sporadic inclusion body myositis. The extensor muscles in the forearms also become affected, followed by involvement of more proximal arm muscles.<sup>e434,e436,e441</sup> Mild neck flexor weakness was noted in some patients (number not



mentioned), and facial weakness was noted in 2/55 families in one study.<sup>e436</sup> Bulbar and extraocular muscles were spared.<sup>e434</sup> The heart was not typically involved, but dilated cardiomyopathy developed in 2 patients late in their course.<sup>e433</sup> Serum CK levels were normal or mildly to moderately elevated (2- to 6-fold).<sup>e436,e441</sup> Muscle ultrasound of 6 patients demonstrated severe atrophy of the hamstring, anterior tibial, and peroneal muscles with milder quadriceps and gastrocnemius involvement and central atrophy with peripheral sparing; the “myopathic target” was noted in all 6 patients in the hamstrings.<sup>e435</sup> Muscle biopsy demonstrated dystrophic myopathy and rimmed vacuoles. The autophagic vacuoles had nuclear and cytoplasmic 15- to 18-nm filamentous inclusions on EM.<sup>e437-e439,e441-e443</sup> Perivascular lymphocytic inflammation was described in 1/55 families in one study.<sup>e436</sup>

*Autosomal dominant hIBM with Paget disease and frontotemporal dementia (hIBMPFD) (valosin-containing protein or VCP).* Seventeen Class III studies were reviewed and are summarized here.<sup>e445-e461</sup> Pedigrees included Asian, North American, European, Scottish, British, and Australian families. The myopathy was variably associated with Paget disease of bone (PDB), frontotemporal dementia, and more recently motor neuron disease (familial amyotrophic lateral sclerosis [fALS]). There was significant heterogeneity in clinical phenotype and severity both between and within families. Age at onset was variable, but across studies the mean age at onset for myopathy and PDB was 43 years (range late 20s–81 years). Most patients presented with either limb-girdle or scapuloperoneal weakness. A purely distal myopathy affecting lower and upper extremities was reported a Finnish kindred.<sup>e461</sup> Scapular winging and lumbar lordosis were common. Frontotemporal dementia was described in approximately 30%–50% of patients, with onset approximately 10 years after weakness (average age 54 years). PDB tended to occur

earlier than in sporadic PDB and was seen with variable frequency, ranging from 29% to 100% in various kindreds; in some patients, PDB was not clinically apparent but was diagnosed by laboratory and radiographic findings. In a British pedigree, dilated cardiomyopathy (4/18 patients), urge incontinence (5/5 patients), and fecal incontinence (4/5 patients) were described.<sup>e451</sup>

CK levels were normal or slightly elevated (<10-fold). Elevated blood alkaline phosphatase was found with high frequency among patients with PDB (86% average across the studies [range 57%–100%]). Muscle MRI in 2 studies<sup>e451,e454</sup> showed symmetric fatty degeneration of the quadriceps/hamstrings/glutei and anterior/posterior compartment of the legs. In the upper extremity, MRI showed fatty degeneration of paraspinal, supraspinatus, infraspinatus, and teres minor, and less so biceps, triceps, and deltoid.

Characteristic findings on muscle biopsy included rimmed vacuoles with ubiquitin and VCP-positive cytoplasmic inclusions, although in the larger series these were noted in less than half of biopsies (33%–39%).<sup>e447,e448,e460</sup> Most biopsies revealed nonspecific myopathic abnormalities as well as neurogenic features of type grouping and angulated fibers. The latter may be due to FALS that can be associated with VCP mutations.<sup>e447,e448,e460</sup> EM showed paired helical filaments in muscle and in PDB osteoclasts.<sup>e460</sup>

*Fast myosin heavy chain, MYHC-IIA, IBM3.* Five Class III studies were reviewed.<sup>e462-e466</sup> Since some of the Swedish studies<sup>e463,e465</sup> appeared to report the same patients, they were reviewed along with Martinsson et al.,<sup>e466</sup> the original study. This disorder has been reported in Sweden, Finland, and the United Kingdom.<sup>e463,e464,e466</sup> Age at onset ranged from birth to 40 years.<sup>e463,e464</sup> Myalgia and muscle weakness were the presenting symptoms in 7/15 patients in one family<sup>e463</sup>

and were common in the first report of 19 patients as well, although numbers were not provided.<sup>e466</sup> Muscle weakness was predominantly proximal in a limb-girdle distribution. External ophthalmoplegia was a consistent finding in all 19 patients of one family in the initial report. They were found to have a dominant missense mutation, p.E706K,<sup>e466</sup> but ophthalmoplegia was not described in a second report of 8 patients who had different missense mutations in the *MYHC-IIA* gene. In patients in whom the disease started at birth, congenital joint contractures were seen.<sup>e465,e466</sup> Hand and face weakness were noted in 7/19 patients, and congenital hip dislocation in 4/19.<sup>e466</sup> Mild cervicothoracic kyphoscoliosis was described in 3/15 patients in one study<sup>e463</sup> and 7/19 in the original description of one family.<sup>e466</sup> Finally, one study described 5 patients with nonsense or truncating mutations from 3 families, one from the United Kingdom and 2 from Finland.<sup>e464</sup> Three presented in early childhood; 2 were asymptomatic. All had pronounced ophthalmoplegia, ptosis, and facial muscle weakness. Neck flexors were weak in 3/5, elbow flexors and ankle dorsiflexors were weak in 2, and 3 had joint hypermobility. Serum CK levels were normal in all 3 patients in whom they were checked. Two patients had muscle MRI that showed moderate diffuse fatty degenerative changes in the thigh and medial gastrocnemius. Muscle biopsy in the initial description revealed small and infrequent type II fibers, focal disorganization of the myofibrils, and rimmed vacuoles and inclusion consisting of 15- to 20-nm tubulofilaments.<sup>e466</sup> One muscle biopsy had lobulated fibers and another had central nuclei and minicores in another study of patients with a different missense mutation.<sup>e463</sup> Finally, in patients with the nonsense or truncating mutation, muscle biopsies demonstrated the absence of type II A fibers and myopathic changes.<sup>e464</sup> Thus, different mutations in the *MYH-IIA* gene appear to have different clinical presentations and muscle biopsy features.

***Distal muscular dystrophies/myopathies. Welander distal myopathy.*** Six Class III studies were reviewed.<sup>e263,e467-e471</sup> Although most often seen in the Swedish population,<sup>e468</sup> Finnish patients with Welander distal myopathy have also been described.<sup>e471</sup> This myopathy was recently reported to be caused by mutations in the RNA-binding protein described initially as T-cell restricted intracellular antigen (TIA1), now known to be expressed widely.<sup>e472</sup> The age at onset ranged from 24–60 years across studies, with a mean in the third to fourth decade of life.<sup>e263,e468-e471</sup> The weakness predominantly involved the finger extensors and foot dorsiflexors and often began in either the hands or the legs. All 7 patients had foot dorsiflexor weakness in one study.<sup>e467</sup> All 9 patients in another study had finger extensor weakness, and 7/9 patients had foot dorsiflexor weakness.<sup>e468</sup> In a third study, 2/4 patients had finger extensor weakness, 1/4 had both finger extensor and foot dorsiflexor weakness, and the remaining 1/4 had weakness limited to foot dorsiflexors.<sup>e470</sup> Thenar muscle atrophy was noted in 3/4 patients in one study.<sup>e470</sup> An unusual feature of Welander myopathy is impaired distal sensation<sup>e468,e469,e471</sup>; however, nerve conduction studies were normal in all patients in one study.<sup>e469</sup> CK levels were normal in 3/4 patients and mildly elevated (<10-fold) in 1/4 patients.<sup>e263,e470</sup> Imaging studies (CT and MRI) revealed fatty infiltration in the tibialis anterior, gastrocnemius, and soleus muscles with relative sparing of the peroneus and tibialis posterior muscles.<sup>e263,e467,e471</sup> In the proximal leg, the biceps femoris, semitendinosus, semimembranosus, and adductors were involved. Muscle biopsy revealed rimmed vacuoles mainly in atrophic fibers but also less frequently in normal fibers when performed in the distal muscles such as the tibialis anterior.<sup>e468-e471</sup> In contrast, biopsy of a proximal muscle such as the vastus lateralis was normal in 7/7 patients in one study.<sup>e467</sup> EM revealed cytoplasmic 16- to 21-nm filaments associated with the rimmed vacuoles. Other abnormalities included dense collections of Z-disk material or

streaming, double Z-disks, honeycomb material, and abnormal mitochondria.<sup>e470</sup> Moderate loss of myelinated nerve fibers was noted in 2/5 patients in one study.<sup>e469</sup>

*Markesbery-Griggs distal muscular dystrophy.* This is discussed in the MFM section under *ZASP*.

*Udd distal muscular dystrophy.* This is discussed in the section on LGMD2J and HMERF (titinopathy).

*Miyoshi distal myopathy.* This is discussed in the sections on LGMD2B (dysferlin) and LGMD2L (anoctamin-5).

*Nonaka distal myopathy.* This is discussed in the section on AR-hIBM/*GNE*.

*Laing myopathy/MYH7.* Eleven Class III studies were reviewed.<sup>e473-e483</sup> Mastaglia et al.<sup>e475</sup> is a follow-up of the kindred described in Laing et al.<sup>e478</sup>; these are reviewed together. Disorders caused by myosin heavy chain (*MYH7*) mutations have been classified into 2 subgroups with distinct clinical and pathologic findings: Laing distal myopathy (LDM) and hyaline body (or myosin storage) myopathy. In LDM, the typical clinical features are of an early-onset distal myopathy, with weakness and atrophy beginning in the first decade and selectively involving the anterior compartment of the lower leg, including ankle and toe dorsiflexors, resulting in foot drop or “hanging big toe.” Weakness progresses slowly, with an average of 10 years before involvement of finger extensors and neck flexors, and later development of proximal extremity

weakness.<sup>e474,e475,e478,e483</sup> Neck flexor weakness is a distinguishing feature from other distal myopathies and was reported in 20%–100% of cases in various series.<sup>e474,e478,e483</sup> Mild facial weakness was described in up to 70% of patients.<sup>e475,e477</sup> Calf hypertrophy was noted in 11/31 (35%) in the largest cohort of patients.<sup>e477</sup> Scapular winging was observed in 2/9 (22%) and 4/31 (13%) patients in the largest cohorts.<sup>e477,e478</sup> Disabling myalgias were a clinical feature in 33% of 31 patients.<sup>e477</sup> Associated findings of scoliosis, pes cavus, ankle contractures, and lumbar hyperlordosis were variably described in about half of 43 patients reported.<sup>e474,e476,e477,e483</sup> One of 27 patients had dilated cardiomyopathy,<sup>e477</sup> but this was atypical; a single patient with a syndrome of hypertrophic cardiomyopathy and tibialis anterior hypertrophy was described.<sup>e480</sup> Skeletal muscle CT scans in 7 patients<sup>e477</sup> and MRI in 28 patients revealed selective early involvement of the toe extensors, anterior tibialis, and sternocleidomastoids.<sup>e474,e477,e478,e483</sup> Muscles from the posterolateral lower leg and rectus femoris were affected at very late stages; the gastrocnemius was spared.<sup>e477</sup> Across studies, serum CK levels were normal or only slightly elevated (<3 times the ULN).<sup>e474,e477,e478,e480</sup> Five studies described muscle biopsies in 21 patients<sup>e474,e477,e478,e480,e483</sup>; these showed variable and often nonspecific myopathic changes, most commonly atrophy and type I fiber grouping. Rimmed vacuoles were typically absent. Myosin immunohistochemistry demonstrated coexpression of slow and fast myosin in type I fibers, highly characteristic of LDM.

Four studies were relevant to myosin storage (hyaline body) myopathy.<sup>e473,e479,e481,e482</sup> Although phenotypes vary considerably, muscle biopsy findings are characteristic for the disorder. Patients presented from the first to the fifth decade, and the average age at onset ranged from 29–38 years.<sup>e479,e481</sup> Weakness in either a scapuloperoneal or a limb-girdle distribution was described; CK levels were normal or slightly elevated.<sup>e473,e479,e481,e482</sup> In a British kindred, limb-girdle

weakness was associated with hypertrophic cardiomyopathy in 3/3 siblings,<sup>e481</sup> but other patients were reported to have normal echocardiography.<sup>e473,e482</sup> Muscle biopsies from 8/8 individuals revealed subsarcolemmal “hyaline bodies”: discrete, amorphous, eosinophilic material in type I fibers exclusively, staining homogeneous pale pink on hematoxylin & eosin and faint green on Gomori, which stains intensely with antibodies to *MHY7*.<sup>e473,e479,e481,e482</sup>

*Vocal cord and pharyngeal weakness with distal myopathy (matrin-3).* Two Class III studies were reviewed.<sup>e484,e485</sup> Two pedigrees were reported: one white North American and one Bulgarian. Mean age at onset of weakness was 45 years. The clinical phenotype was slowly progressive, beginning with foot drop and distal upper extremity muscle weakness and progressing to involve proximal muscles, frequently associated with dysphagia and dysphonia. One patient from the North American pedigree (37 individuals, 12 who underwent clinical examination) had restrictive ventilatory weakness and low EF. None of the patients in this pedigree had unexplained cardiomyopathy. CK levels were slightly elevated (<10 times normal) in 13/17 cases tested and normal in 4/17. Muscle biopsies showed characteristic subsarcolemmal rimmed vacuoles in 5/7; 2/7 biopsies showed end-stage changes.

*Filamin C (Williams distal myopathy).* This is discussed in the MFM section on filamin C (Williams distal myopathy).

*Nebulin (NEB).* Two Class III studies were reviewed.<sup>e486,e487</sup> The first Class III study described 7 patients of Finnish descent from 4 unrelated families with a novel recessively inherited distal myopathy caused by homozygous missense mutations in the nebulin gene.<sup>e486</sup> In the second Class

III study, 3 non-Finnish patients from 2 unrelated families were reported to have distal myopathy caused by 4 different compound heterozygous nebulin mutations. Onset was in early childhood, with very slowly progressive weakness and atrophy of ankle dorsiflexors, finger extensors, and neck flexors, initially presenting with foot drop. Delayed motor milestones (walking at 2 years), an elongated face, and lumbar lordosis were reported in 2 children who presented at ages 11 and 13 years with foot drop.<sup>e487</sup> Mild to moderate facial weakness was noted in 6 of 7 patients (86%). CK levels were normal in 6/7 patients (86%) and slightly elevated in 1/7 patients (14%) in the Finnish study and normal in all 3 patients of non-Finnish descent.<sup>e486,e487</sup> One of 6 patients (17%) demonstrated a low FVC.<sup>e486</sup> Imaging was abnormal in all patients: CT (3/3) and MRI (5/5) of the leg muscles showed fatty degeneration in the anterior compartment of the lower legs.<sup>e486,e487</sup> Muscle biopsies demonstrated nemaline bodies.<sup>e486,e487</sup>

*Distal myopathy with Kelch-like homologue 9 mutations (KLHL9).* One Class III study<sup>e488</sup> reported a German kindred with 10 affected members who had weakness and atrophy of the anterior tibial muscles (age at onset between 8 and 16 years), followed later by atrophy of the intrinsic hand muscles. The disorder was slowly progressive and patients retained the ability to walk until the seventh decade. Ankle contractures were present in all 10 patients. Tendon reflexes were absent in the lower extremities in 2 patients. Reduced sensation in a distal symmetric pattern was noted in 7 patients between the ages of 25 and 67 but not in the younger patients.

CK levels were normal or mildly elevated in 8 patients and moderately elevated (144 U/L) in one. Nerve conduction studies in 2 patients revealed mildly prolonged distal latencies in some motor nerves and reduced sural amplitude in one patient. ECG, echocardiogram, and pulmonary



function tests were normal in one patient. MRI of the lower extremity in the index patient showed symmetric fatty atrophy that was most prominent in the semimembranosus, biceps femoris, and vastus intermedius, whereas the vastus lateralis and medialis, sartorius, gracilis, and adductors were preserved. The tibialis anterior, gastrocnemius, and soleus were more affected than the peroneus longus or tibialis posterior. Muscle biopsy in the index case did not reveal vacuoles. There were dystrophic changes and angulated fibers. There was loss of fiber typing on NADH stain. Sural nerve biopsy did not reveal neuropathy. Immunohistochemistry revealed normal expression of dystrophin, caveolin-3, laminin- $\alpha$ 2, and sarcoglycan-dystroglycan complex. All patients possessed a heterozygous mutation in the *KLHL9* gene encoding a bric-a-brac Kelch protein.

**Other disorders.** *Selenoprotein (SEPNI, rigid spine syndrome).* Most studies reviewed discussed the congenital myopathy phenotype of *SEPNI* mutations and are not included in this guideline. Two Class III studies are reviewed.<sup>e85,e489</sup> One large Class III study<sup>e489</sup> described the clinical course of *SEPNI*-related muscular dystrophy in 41 patients. Mean age at onset was 2.7 years and ranged from birth to the second decade. In 19 of 41 patients (46%), the onset was between 6 months and 5 years, with delayed milestones, difficulty running, or falls. Scoliosis or easy fatigability was noted at onset in 3 children between the ages of 6 and 10 years; 2 presented at 7 years with running difficulty and 2 at age 13 years with back stiffness and generalized muscle weakness and atrophy. CK levels were normal in 29/37, minimally elevated in 6/37, and markedly elevated in only 1/37. Rigid spine was noted in 25 patients and scoliosis in 26 with onset between the ages of 1 and 20 years. Nine patients required spinal surgery by age 15 years, and an additional 4 required it by age 20. Joint contractures were present in 26 patients by the

age of 10 years and involved the Achilles tendon, elbow, and long finger flexors. Mild right ventricular hypertrophy/pulmonary hypertension was found in only 5 patients. Twenty-seven of 41 patients required nocturnal noninvasive ventilation for reduced FVC. Most patients remained ambulatory; only 6 became wheelchair dependent. MRI in 13 children revealed selective or prominent involvement of the sartorius; no selectivity was noted at the calf level.<sup>e85</sup> Muscle biopsy features included nonspecific myopathic change (5/20), type I fiber predominance (5/20), multiminicores (8/20), and cores (2/20); Mallory bodies were noted in one patient who also had nonspecific myopathy.

*Muscular dystrophy with generalized lipodystrophy (cavin-1/polymerase I and transcript release factor [PTRF]).* Three Class III studies were reviewed.<sup>e490-e492</sup> The first study reported 5 Japanese patients of nonconsanguineous parentage with *PTRF* mutations causing a secondary deficiency of caveolin-3.<sup>e490</sup> The second study<sup>e491</sup> reported 15 patients from Oman and one from the United Kingdom. The third study reported 2 Mexican siblings and a Turkish girl with the disorder.<sup>e492</sup> The age range was from the neonatal period to 24 years. All patients had generalized lipodystrophy. Clinical information was incomplete in the second study.<sup>e491</sup> Developmental delay was noted in all 3 patients in one study.<sup>e492</sup> Weakness was present in 12/15 patients in the second study<sup>e491</sup> but not described. In the first study, weakness was distal dominant in 2/5, generalized in one, and absent in the other 2.<sup>e490</sup> Almost all patients had electrically silent percussion-induced muscle mounding, muscle hypertrophy, myalgias, and cramps. Five of the 23 described patients had cardiac arrhythmias, including prolonged QTc syndrome. Sudden death in the teenage years occurred in 4 patients in one study.<sup>e491</sup> Six of 23 patients had hepatosplenomegaly/fatty liver. Across studies, scoliosis was noted in 5 patients, rigid spine in 2, lordosis in one, and

contractures (ankle, finger, and other unspecified) in 6. Fifteen patients had congenital hypertrophic pyloric stenosis. Insulin resistance (4 patients across the studies), elevated serum triglycerides (10), acanthosis nigricans (3), and atlantoaxial dislocation (1) were other features. CK levels were elevated in all patients tested, ranging from 542–2,630 IU/L (<10- to >10-fold). Muscle CT scan in one patient revealed hypertrophy of paravertebral and thigh muscles with minimal subcutaneous and abdominal fat.<sup>e490</sup> Reduced immunoreactivity to *PTRF* antibodies was noted on muscle biopsies. Caveolin-3 immunoreactivity was greatly reduced in the sarcolemma, but cytoplasmic staining was increased in a pattern similar to LGMD caused by caveolin-3 mutations. Immunoblotting revealed absent *PTRF* bands.<sup>e490</sup>

## Conclusion

In patients with LGMD and distal muscular dystrophy, a combination of clinical, radiologic, and laboratory features are useful in directing genetic diagnosis (multiple Class I–III studies). Single features that are pathognomonic of a disorder are seen only rarely (see figures 1–5 in the summary article published in print and figures e-1 and e-2 and table e-2, available as online data supplements).

**Clinical Question 5: Are there effective therapies (medications, gene therapy, exercise, complementary and alternative therapies, orthopedic interventions, surgery) for muscular dystrophies that improve muscle strength, slow the rate of strength decline, preserve ambulation and overall function, delay time to tracheostomy ventilation, maintain healthy EF, slow cardiac mortality, preserve quality of life and activities of daily living, and delay overall mortality?**

There were 12 studies (2 Class I,<sup>e493,e494</sup> 4 Class II,<sup>e495-e498</sup> and 6 Class III<sup>e246,e344,e462,e465,e499,e500</sup>) evaluating treatments for disorders described below. No articles were identified for the other disorders discussed in this guideline.

In a Class II randomized, double-blind, placebo-controlled trial,<sup>e498</sup> adeno-associated virus (*AAV*) gene transfer to the extensor digitorum brevis (EDB) muscle was performed in 6 patients with LGMD2D ( $\alpha$ -sarcoglycanopathy) on one side. Saline was injected into the opposite EDB as a control.  $\alpha$ -Sarcoglycan gene expression increased 4- to 5-fold in 3 subjects (at 6 weeks in 2 subjects and at 12 weeks in the third subject); restoration of the  $\alpha$ -sarcoglycan complex was also noted.<sup>e498</sup> Three subjects were followed for an additional 3 months and reported on in a subsequent Class I study.<sup>e494</sup> Persistent  $\alpha$ -sarcoglycan gene expression was noted at 6 months in 2/3 subjects. One patient failing gene transfer demonstrated an early rise in neutralizing antibody titers and T-cell immunity to *AAV*. No adverse effects (AEs) were reported.<sup>e494</sup>

A Class III study<sup>e500</sup> of 3 patients with LGMD2C who received the highest of 3 escalating doses of *AAV*-vector expressed human  $\gamma$ -sarcoglycan genes ( $4.5 \times 10^{10}$  copies) into the extensor digitorum communis found increased  $\gamma$ -sarcoglycan expression (4.5%–10% positively stained fibers on muscle biopsy) 30 days after injection. One patient had detected  $\gamma$ -sarcoglycan by Western blot as well. Muscle strength was stable over 6 months of follow-up. MRI of the forearm before and 15 days postinjection did not reveal changes. Inflammatory markers did not change and no inflammation was noted on repeat biopsy.

**Conclusion.** *AAV* gene therapy into the EDB muscle of patients with LGMD2D probably increases the expression of  $\alpha$ -sarcoglycan gene and restores the protein complex for up to 6

months postinjection without significant AEs (one Class I and one Class II study). Data are insufficient to determine the effect of *AAV*-vector expressed  $\gamma$ -sarcoglycan genes in patients with LGMD2C (one Class III study).

***Clinical context.*** These are small proof-of-concept studies. Despite increased expression of the target protein in these few patients, the clinical relevance of gene therapy is yet to be determined. Other considerations include the number of injection sites and frequency of injection.

A Class I phase 1/2 randomized, double-blind, placebo-controlled trial evaluated the safety and tolerability of a neutralizing antibody to myostatin (MYO-029), which is an endogenous inhibitor of muscle growth.<sup>e493</sup> Four dosing cohorts of 36 patients each (total 116 subjects: 36 BMD; 38 LGMD2A, 2B, 2C, 2D, 2E, and 2I; 42 facioscapulohumeral dystrophy) were included in the trial. The dosing cohorts were 1 mg/kg, 3 mg/kg, 10 mg/kg, and 30 mg/kg intravenously every 2 weeks for 6 months, for a total of 13 doses. Subjects were followed for 3 months after the last dose. MYO-029 was found to be safe and well tolerated. One hundred four of 116 subjects (89%) reported AEs. The only AE that was significantly more common in the treatment group was accidental injury (8/27 [27.6%] in the placebo group and 13/27 [48%], 11/27 [41%], and 4/27 [15%] in the 1, 3, and 10 mg/kg cohorts, respectively,  $p = 0.026$ ). The major AE was cutaneous hypersensitivity, seen in 4/27 patients (15%) in the 10 mg/kg group and 2/6 patients (33%) in the 30 mg/kg cohort. Rash and urticaria were noted in 12 subjects in all (2/29 [7%] in the placebo group, 3/27 [11%] in the 1 mg/kg group, 1/27 [3.7%] in the 3 mg/kg group, 4/27 [15%] in the 10 mg/kg group, and 2/6 [33%] in the 30 mg/kg group). Seven subjects (6%) had serious AEs (2/29 patients [6.9%] in the placebo group, 2/27 [7.4%] in the 3 mg/kg group [one

patient with dementia and one with depression followed by suicide attempt], and 3/27 [11.1%] in the 10 mg/kg cohort [one case of diplopia and unconfirmed aseptic meningitis, one case of diarrhea, and one case of chest pain]). No deaths were reported. The 30 mg/kg cohort was discontinued due to cutaneous hypersensitivity. No improvement was noted in muscle strength, but a trend toward increase in lean body muscle mass using dual-energy x-ray absorptiometry was noted in the 3 mg/kg group (placebo  $-0.07 \pm 0.7$ , 3 mg/kg  $2.4 \pm 0.7$ ,  $p = 0.05$ ). The study was not powered to assess efficacy.<sup>e493</sup>

**Conclusion.** Neutralizing antibody to myostatin (MYO-029) is probably safe and tolerable in patients with BMD and LGMD2A–E and 2I at doses of 1 and 3 mg/kg, although a few serious side effects were noted which require further research. Cutaneous hypersensitivity is noted at 10 and 30 mg/kg doses. There are no data regarding long-term safety. There is probably a trend toward increase in lean body muscle mass, but the study was not powered to assess efficacy (one Class I study).

A 12-month randomized, double-blind, placebo-controlled Class II study<sup>e495</sup> evaluated the efficacy of prednisolone 0.35 mg/kg/day for 6 months with crossover to placebo for 6 months in 4 boys with BMD. Isometric muscle strength at 3 months increased by 139% with prednisolone ( $p < 0.001$ , corrected for multiple outcomes) but was nonsignificant at 6 months. Three of the 4 patients showed stable or improved muscle strength on prednisolone. Two of the 4 patients improved or stabilized on placebo and 1/4 deteriorated on placebo. The difference was nonsignificant by  $\chi^2$  test. Although improvements were noted in ankle and wrist dorsiflexors and elbow extensors at 3 months and in knee flexors and neck extensors at 3 and 6 months, these

differences were nonsignificant when the authors corrected for multiple outcomes. The study was underpowered to detect a significant improvement or to exclude benefit in other outcomes.<sup>e495</sup>

**Conclusion.** On the basis of one Class II study, prednisolone 0.35 g/kg/day is probably effective to improve isometric muscle strength in patients with BMD after 3 months of treatment.

A Class III study<sup>e496</sup> evaluated myoblast transplantation into the tibialis anterior in 3 males with BMD compared with saline injections into the opposite tibialis anterior. Patients were pretreated with cyclosporine A (CyA) for 2 months prior to transplantation and continued it for a year posttransplantation. Force generation in the tibialis anterior was measured bilaterally at baseline, after 2 months of CyA, after myoblast implantation, and after discontinuation of CyA. CyA alone produced a significant bilateral increase in muscle force pretransplantation in one patient, and another patient had significant bilateral increase in tibialis anterior force on CyA posttransplantation, but because the increase was bilateral it was felt to be unlikely to be due to the transplant. None of the biopsies showed dystrophin level changes that could be considered therapeutic.<sup>e496</sup>

**Conclusion.** On the basis of one Class III study, data are inadequate to support or refute the use of myoblast transfer in BMD.

A randomized double-blind Class III study<sup>e497</sup> evaluated the effects of self-injected subcutaneous growth hormone (GH) 0.07 mg/kg/week for 3 months in 10 patients with BMD. The

cardiomyopathic index (echocardiogram QT:PQ ratio) did not change significantly. The complexity of ventricular premature beats as assessed by the Lown classification system decreased from 4A to 1A in 1/6 patients treated with GH and from 4B to 4A in 1/4 patients treated with placebo. In patients treated with GH, left ventricular mass assessed by echocardiogram increased by 42 g (baseline  $150 \pm 14$ , 6 weeks  $163 \pm 27$ , 12 weeks  $173 \pm 27$ ,  $p < 0.05$ ) and reduced nonsignificantly in controls. Relative wall thickness also increased by 12% (baseline  $0.23 \pm 0.01$ , 6 and 12 weeks  $0.05 \pm 0.01$ ,  $p < 0.05$ ), and end-systolic wall stress dropped by 13% in patients treated with GH (baseline  $168 \pm 19$ , 6 weeks  $149 \pm 14$ , 12 weeks  $146 \pm 15$ ,  $p < 0.05$ ) without change in controls. Plasma levels of brain natriuretic peptide, which were elevated when compared with normal values, decreased by 40% in the active treatment group, whereas no significant changes were detected in the placebo group (GH baseline  $\pm$  SE  $190 \pm 60$  ng/mL, 12 weeks  $114 \pm 50$ ,  $p < 0.05$ ; placebo baseline  $205 \pm 45$ , 12 weeks  $210 \pm 55$ ). Timed functional tests and pulmonary function did not change significantly between groups over 12 weeks. No AEs were noted.<sup>e497</sup>

**Conclusion.** Data are inadequate to support or refute the use of subcutaneous GH injections to improve cardiac and pulmonary function in patients with BMD (one Class III study).

A Class III study<sup>e499</sup> evaluated a hand training program consisting of 3 weekly sessions of resistance and stretching exercises (2 self-training, one guided by an occupational therapist) in 12 patients with Welander distal myopathy. There was a one-grade increase in right hand strength on manual muscle testing in 7/12 patients and a 2-grade increase in 1/12. There was also an increase in peak pre-/post-pinch grip as measured by Grippit in 11/12. Range of motion



measured with a finger goniometer increased from -470 degrees in the right hand and -790 in the left hand to -260 and -510 degrees, respectively. Self-reported performance of activities of daily living improved in multiple domains. When corrected for multiple outcomes, none of these changes was significant. Mean pre-/post-pinch grip scores, grip strength measured with Grippit, and life satisfaction score changes were also nonsignificant.<sup>e499</sup>

**Conclusion.** On the basis of one Class III study, data are insufficient to support or refute the benefit of a hand exercise program in WELANDER distal myopathy.

Another Class III study<sup>e246</sup> evaluated the effect of endurance training in 9 ambulatory patients with LGMD2I and 9 healthy, sedentary, age-matched controls. The home training program consisted of 30-minute stationary bicycle ergometer exercise sessions at a heart rate corresponding to 65% of maximal oxygen uptake (VO<sub>2</sub> max) for 12 weeks. The number of sessions increased progressively for the first 4 weeks to 5 times a week in the last 8 weeks. In the patients, VO<sub>2</sub> max and maximal workload (Wmax) increased by 21% and 27%, respectively, at 12 weeks ( $p < 0.0005$ ). These parameters also increased in the control group, but there was no difference in the absolute increase between groups. Plasma lactate and heart rate did not change before and after training. Self-reported improvement was noted in physical endurance (8/9 patients), leg muscle strength (7/9), and walking distance (6/9). Capillary density increased on the 5 tested muscle biopsies (mean  $\pm$  SE before:  $209 \pm 19 \text{ mm}^2$ , after:  $255 \pm 30 \text{ mm}^2$ ,  $p = 0.05$ ). CK levels and mean muscle type II fiber area showed a trend toward increase in 5/9 patients with LGMD2I tested at 12 weeks (CK levels before:  $661 \pm 154$ , after:  $1,068 \pm 298$ ,  $p = 0.08$ ; type II fiber area before:  $7,604 \pm 735 \text{ mm}^2$ , after:  $8,982 \pm 1,204 \text{ mm}^2$ ,  $p = 0.09$ ). There were no AEs.<sup>e246</sup>

**Conclusion.** Data are insufficient to support or refute the benefit of endurance training for 12 weeks to improve VO<sub>2</sub> max, Wmax, and patient-reported outcomes of leg strength, physical endurance, and walking distance in patients with LGMD2I (one Class III study).

A Class III study by the same authors evaluated endurance training in 11 men with BMD and 7 healthy sedentary men.<sup>e344</sup> The exercise protocol was similar to that of the previous study.<sup>e246</sup> Six patients continued the protocol 3 times weekly for 12 months. At 12 weeks VO<sub>2</sub> max and Wmax improved by 47% and 80%, respectively ( $p < 0.005$ ), which was 3–4 times higher than the changes in controls. Plasma lactate levels and heart rate were not significantly different. A significant increase in muscle strength of the hip abductors and foot dorsiflexors and plantarflexors was also noted; this was maintained at 12 months (increase in strength [Newtons, mean  $\pm$  SE]: hip abductors  $22 \pm 7\%$ , foot dorsiflexors  $13 \pm 6\%$ , foot plantarflexors  $20 \pm 4\%$ ,  $p < 0.05$ ). At 12 months there was a 40% increase in quadriceps strength as well (hip abduction  $13 \pm 7\%$ , hip flexion  $14 \pm 8\%$ , knee extension  $40 \pm 15\%$ , foot dorsiflexion  $25 \pm 5\%$ , foot plantarflexion  $21 \pm 5\%$ ,  $p < 0.05$ ). In one patient LVEF increased from 35% to 50% at 12 months. LVEF did not change in any of the other patients. A “majority” of patients with BMD reported improvement in physical endurance, leg muscle strength, and walking distance after 12 weeks of training. CK levels, lean body mass, and body fat percentage did not change. No changes were noted in muscle fiber diameter or capillary density. In the 6 patients who continued the endurance program for 12 months, the improvement in VO<sub>2</sub> max, Wmax, and muscle strength was sustained but did not improve further. In 1/3 patients tested, cardiac EF increased from 35% to 50% at 12 months.<sup>e344</sup>

**Conclusion.** Data are insufficient to determine the effect of 12 weeks of endurance training for improving VO<sub>2</sub> max, Wmax, muscle strength, and patient-reported outcomes of physical endurance, leg muscle strength, and walking distance in patients with BMD (one Class III study).

Two Class III studies<sup>e462,e465</sup> evaluated the effects of exercise on hIBM3 secondary to a defect in the *MYH2* gene. In the first study,<sup>e462</sup> 8 patients participated in an 8-week home exercise program for 30 minutes/day, 5 days a week on a stationary bicycle. No improvements were seen in any of the outcomes after correction for multiple outcomes. The same authors studied 6 patients from the same families after a similar exercise protocol.<sup>e465</sup> Maximal workload increased in all patients (statistical data not provided), and expression of MYH IIx and increase in MYH types I and IIa were noted on postexercise biopsies of the vastus lateralis compared to pre-exercise biopsies ( $p < 0.05$ ). There was no change in muscle strength of the knee extensors and flexors.

**Conclusion.** Data are inadequate to assess the effect of endurance training on maximum workload, muscle strength, or change in the expression of myosin isoforms on muscle biopsy in hIBM3 (2 conflicting Class III studies).

## **RECOMMENDATIONS FOR THE DIAGNOSIS, EVALUATION, AND MANAGEMENT OF LIMB-GIRDLE AND DISTAL MUSCULAR DYSTROPHIES**

The recommendations below encompass 3 major areas: diagnosis, evaluation, and management of muscular dystrophies, including limb-girdle, humeroperoneal, and distal muscular

dystrophies. Each recommendation is preceded by clinical context that outlines the evidence, general principles of care, and evidence from related disorders that drive the recommendations.

Key:

EVID: Statements supported directly by the systematically reviewed evidence.

PRIN: An accepted axiom or principle.

RELA: Statements supported by strong evidence not included in the systematic review.

INFER: An inference from one or more of the other statements.

Note: Given the relative paucity of literature directly relevant to LGMDs for some of the clinical questions, some of the recommendations below are based in part on evidence from other neuromuscular disorders, primarily amyotrophic lateral sclerosis (ALS).

## **Overall management**

***Clinical context.*** Our systematic review has highlighted the medical complexity of caring for patients with muscular dystrophy (EVID). Such patients may develop cardiac, pulmonary, nutritional, and musculoskeletal complications that require the assistance of cardiologists, pulmonologists, orthopedists, physiatrists, physical therapists, occupational therapists, nutritionists, orthotists, and speech pathologists, in addition to neurologists (INFER). In addition, myopathies with a limb-girdle, humeroperoneal, or distal pattern of weakness may be challenging to diagnose (INFER). A specific diagnosis provides patients with “closure,” assists genetic counseling, and directs monitoring for complications and optimal management (PRIN).

## **Recommendation.**

A00. Clinicians should refer patients with suspected muscular dystrophy to neuromuscular centers to optimize the diagnostic evaluation and subsequent management (Level B).

**Diagnosis of muscular dystrophies (see also table e-2 and figures 1–5, e-1, and e-2)**

**Clinical context.** Our evidence-based review found that muscular dystrophies have some characteristic features, including a predilection for certain ethnicities, type of inheritance (autosomal dominant, recessive, or X-linked), patterns of weakness (limb-girdle, humeroperoneal, or distal), hypertrophy or atrophy of specific muscle groups, and ancillary characteristics such as scapular winging, level of serum CK, particular EMG abnormalities (e.g., myotonic discharges), cardiac and respiratory involvement, and characteristic features on muscle biopsy (e.g., rimmed vacuoles, myofibrillar myopathy, reducing bodies). Very few features were pathognomonic of a specific disorder; for example, a history of PDB, frontotemporal dementia, or motor neuron disease is pathognomonic of hIBMPFD due to mutations in the gene for VCP. Similarly, the likelihood of genetic diagnosis for the dystroglycanopathies (LGMD2K, LGMD2M, LGMD2N, LGMD2O, and LGMD2P) increases in the presence of abnormalities on brain MRI and abnormal  $\alpha$ -dystroglycan immunostaining on muscle biopsy. In most of the other muscular dystrophies reviewed, a constellation of features narrows the differential diagnosis to a few disorders (EVID). The predisposition of certain ethnicities to specific disorders was noted (EVID). However, many disorders are described in several ethnic groups, making it difficult to use ethnicity alone to arrive at a diagnosis. Therefore, in conjunction with specific clinical patterns, certain ethnicities may help to narrow the differential diagnosis and direct confirmatory testing in a proportion of patients (INFER). The limb-girdle and distal muscular dystrophies are

presumed to have genetic origins because no plausible environmental cause has been identified. Sporadic cases may be due to autosomal dominant, recessive, or X-linked inheritance (PRIN).

The accurate diagnosis of the muscular dystrophies is important for patients, their families, and for efficient and cost-effective use of medical resources (INFER). Knowing the specific type of muscular dystrophy assists in defining the long-term prognosis, since some dystrophies are more rapidly progressive, involve the cardiorespiratory systems more frequently, or are associated with other disorders (EVID). The identification of these dystrophies through genetic testing will not only inform long-term prognosis but will also assist in directing care more efficiently (e.g., more frequent cardiorespiratory monitoring and prophylactic treatments such as pacer/defibrillator placement for those disorders known to be associated with cardiac involvement) (INFER). Precise identification of the disorder also eliminates the need for repeated testing for an acquired, treatable disorder such as an inflammatory myopathy, because some dystrophies can have inflammation on muscle biopsy, making diagnosis difficult on the basis of routine biopsy findings alone (INFER). In addition, the temptation to try immunosuppressive agents repeatedly, looking for a therapeutic response, is not unusual when there is no diagnosis and the patient is worsening (INFER). This exposes patients to potentially serious side effects of immunosuppressive medications (PRIN). Patients on immunosuppressants need to be monitored at regular intervals, adding logistical difficulties to a population that may have significantly impaired mobility (INFER). Health care costs are also increased by repeated investigations, immunosuppressive treatments, and laboratory monitoring (PRIN). Although establishing a genetic diagnosis is expensive on the front end, the costs of continued investigation for other causes and the risks and expenses associated with empiric trials of

immunosuppressants make a strong case for establishing a genetic diagnosis, which often provides patients a sense of “closure” (INFER). Establishing a genetic diagnosis is crucial for genetic counseling of families to inform decision making about having children and for screening of offspring based on the genetics of the disorder (PRIN). Treatment of cardiomyopathy, arrhythmias, and ventilatory failure prolongs life and improves quality of life in patients with other neuromuscular diseases (RELA).<sup>e43,e501-e505</sup> The recommendations below also discuss the overall differential diagnosis of LGMD syndromes, including Pompe disease (acid  $\alpha$ -glucosidase deficiency) and the collagen VI disorders, Ullrich and Bethlem myopathy, which may mimic LGMD or EDMD, respectively. These disorders were not formally reviewed in the evidence since they are not included under LGMD, but they should be considered in the differential diagnosis of LGMD and EDMD.

### ***Recommendations.***

A0. For patients with suspected muscular dystrophy, clinicians should use a clinical approach to diagnosis based on the clinical phenotype, including the pattern of muscle involvement, inheritance pattern, age at onset, and associated manifestations (e.g., early contractures, cardiac or respiratory involvement) (Level B).

#### *Limb-girdle pattern of weakness (see figures 3–5).*

A1. In patients with limb-girdle weakness and suspected muscular dystrophy with probable autosomal dominant inheritance, cardiomyopathy, respiratory involvement, EMG with myotonic or “pseudomyotonic” discharges (the latter characterized by runs of decrescendo positive sharp wave discharges without the typical waxing and waning of amplitudes and frequencies seen in

myotonic discharges), ankle dorsiflexor weakness (foot drop), and muscle biopsy (if performed) showing features of myofibrillar myopathy, clinicians should perform genetic testing for mutations in the genes for desmin (LGMD1E), myotilin (LGMD1A), DNAJB6 (LGMD1D), ZASP, filamin C,  $\alpha$ B-crystallin, and titin (Level B).

A2. In patients with limb-girdle weakness and suspected muscular dystrophy with probable autosomal dominant inheritance, rippling muscles, and percussion-induced rapid contractions, clinicians should perform genetic testing for mutations in the caveolin-3 gene (LGMD1C) (Level B).

A3. In patients with limb-girdle weakness and suspected muscular dystrophy with probable autosomal dominant inheritance, early humeroperoneal weakness, contractures (neck, elbows, knee, ankle), and cardiomyopathy, clinicians should perform genetic testing for mutations in the lamin A/C gene (LGMD1B or AD-EDMD) (Level B).

A4. In patients with limb-girdle weakness and suspected muscular dystrophy with probable autosomal dominant inheritance, distal weakness, myotonic discharges on EMG, past or family history of Paget disease, frontotemporal dementia, or motor neuron disease, clinicians should perform genetic testing for mutations in *VCP* (hIBMPPFD) (Level B).

A5. In patients with limb-girdle weakness and suspected muscular dystrophy who either do not have clinical features to suggest a specific form of dystrophy or in whom initial genetic testing is not informative, clinicians should perform muscle biopsy in order to delineate characteristic



features that direct further genetic testing (such as immunohistochemistry/immunoblotting for various sarcolemmal proteins, calpain-3, or features of myofibrillar myopathy; see figures 3–5) or to exclude an alternative diagnosis (e.g., a metabolic myopathy, mitochondrial myopathy, congenital myopathy, or inflammatory myopathy) (Level B).

A6. In patients with limb-girdle weakness and suspected muscular dystrophy with probable autosomal recessive inheritance, scapular winging but no calf hypertrophy, and normal cardiorespiratory function, clinicians should perform initial genetic testing for mutations in calpain-3 (LGMD2A). Patients of English, French, Spanish, Italian, Portuguese, or Brazilian descent may have a higher pretest probability of this disorder (Level B).

A7. In patients with limb-girdle weakness and suspected muscular dystrophy with probable autosomal recessive inheritance and calf atrophy and weakness (i.e., inability to stand on toes), clinicians should perform genetic testing for mutations in anoctamin-5 (LGMD2L) or dysferlin (LGMD2B). If the onset of symptoms is in the teens or early 20s or the patient is from Asia, clinicians should assess for dysferlin mutations first and, if negative, test for anoctamin-5 mutations. If the onset of symptoms is in the 30s or later or the patient is of English or northern European ancestry, clinicians should assess for anoctamin-5 mutations first and, if negative, test for dysferlin mutations (Level B).

A8. In patients with limb-girdle weakness and suspected muscular dystrophy with probable autosomal recessive inheritance and muscle biopsy immunohistochemistry showing reduction in

$\alpha$ -,  $\beta$ -,  $\gamma$ -, or  $\delta$ -sarcoglycans, clinicians should perform genetic testing for mutations in the sarcoglycan genes (LGMD2C–2F) (Level B).

A9. In patients with limb-girdle weakness and suspected muscular dystrophy with probable autosomal recessive inheritance who are of Hutterite descent, clinicians should perform genetic testing for mutations in *TRIM32* (LGMD2H) (Level B).

A10. In patients with limb-girdle weakness and suspected muscular dystrophy with probable autosomal recessive inheritance, scapular winging, calf hypertrophy, and early cardiorespiratory involvement, clinicians should perform initial genetic testing for mutations in *FKRP* (LGMD2I). Patients of northern European descent may have a higher pretest probability of this disorder (Level B).

A11. In patients with limb-girdle weakness and suspected muscular dystrophy with probable autosomal recessive inheritance and mental retardation, clinicians should screen for mutations in genes that cause primary or secondary deficiency of  $\alpha$ -dystroglycan (LGMD2K, LGMD2M, LGMD2N, LGMD2O, and LGMD2P) (Level B).

A12. In patients with limb-girdle weakness and suspected muscular dystrophy with probable autosomal recessive inheritance and epidermolysis bullosa or pyloric atresia, clinicians should perform genetic testing for mutations in plectin (Level B).

A13. In male patients with limb-girdle weakness and suspected muscular dystrophy with probable X-linked inheritance, clinicians should perform genetic testing for mutations in the dystrophin gene (Duchenne or Becker muscular dystrophy) (Level B).

A14. In patients with limb-girdle weakness and suspected muscular dystrophy with probable autosomal recessive inheritance and no other specific clinical features or in whom muscle biopsy does not inform genetic testing, clinicians should perform dried blood spot test for  $\alpha$ -glucosidase (acid maltase) deficiency or Pompe disease (Level B).

A15. In female patients with limb-girdle weakness and suspected muscular dystrophy with probable X-linked inheritance, clinicians should perform genetic testing for dystrophin mutations or perform a muscle biopsy and immunostain for dystrophin to assess for a mosaic pattern of staining. If abnormal immunostaining is present, clinicians should confirm the diagnosis of manifesting carrier of dystrophinopathy with genetic testing for mutations in the dystrophin gene (Level B).

*Humeroperoneal weakness (figure e-1).*

B1. In patients with humeroperoneal weakness and suspected muscular dystrophy with probable autosomal dominant inheritance, early cardiac involvement, and no joint laxity, clinicians should perform genetic testing for mutations in the lamin A/C gene (AD-EDMD, LGMD1B). If the inheritance pattern is probably X-linked, clinicians should perform genetic testing for mutations in the emerin gene (XR-EDMD) (Level B).

B2. In patients with humeroperoneal weakness and suspected muscular dystrophy with early cardiac involvement and no joint laxity who do not possess mutations in the lamin A/C or emerin gene, clinicians should perform muscle biopsy to delineate characteristic abnormalities that direct further genetic testing (see figure e-1 for muscle biopsy features that direct genetic testing) (Level B).

B3. In patients with humeroperoneal weakness and suspected muscular dystrophy with probable autosomal dominant inheritance, joint laxity, protuberant calcaneus, and no cardiac involvement, clinicians should perform genetic testing for mutations in the collagen VI gene (Bethlem myopathy). If the inheritance pattern is probably autosomal recessive with congenital onset, clinicians should perform genetic testing for mutations in the collagen VI gene (Ullrich myopathy) (Level B).

*Distal muscular dystrophy (figure e-2).*

C1. In patients with late adult onset of index finger and wrist extensor weakness followed by atrophy and weakness of hand muscles and muscle biopsy showing rimmed vacuoles, clinicians should make a diagnosis of Welander distal myopathy. Patients of Swedish or Finnish descent may have a higher pretest probability of this disorder. Clinicians should confirm the diagnosis with genetic testing for Welander myopathy when testing becomes commercially available (Level B).

C2. In patients with suspected distal muscular dystrophy and probable autosomal recessive inheritance with early onset of calf weakness, clinicians should perform genetic testing for

mutations in the anoctamin-5 and dysferlin genes. If the patient is of northern European descent, clinicians should perform initial genetic testing for mutations in the anoctamin-5 gene (LGMD2L) and, if negative, perform genetic testing for mutations in the dysferlin gene (LGMD2B). If the patient is from eastern Asia (Japan, China, Korea), clinicians should perform initial genetic testing for mutations in the dysferlin gene (LGMD2B, Miyoshi myopathy) and, if negative, perform genetic testing for mutations in the anoctamin-5 gene (LGMD2L) (Level B).

C3. In patients with suspected distal muscular dystrophy and probable autosomal recessive inheritance with early onset (<30 years of age) of progressive foot drop who are of Japanese or Middle Eastern Jewish descent, clinicians should perform initial genetic testing for *GNE* mutations (AR-hIBM) (Level B).

C4. In patients with suspected distal muscular dystrophy without the clinical features in C2 or C3 above, clinicians should perform a muscle biopsy to direct further genetic testing (see figure e-2 for biopsy and clinical features that direct genetic testing) (Level B).

*Other diagnostic considerations.*

D1. In patients with muscular dystrophy who have proximal as well as distal weakness, clinicians should use specific clinical features (e.g., rippling muscles, cardiomyopathy, atrophy of specific muscle groups, irritability on EMG) and biopsy features (MFM, reduction of emerin immunostaining, presence of rimmed vacuoles) to guide genetic testing, which may include mutations in the genes causing the various forms of MFM (see section on MFM), LGMD2B

(dysferlin), LGMD2L (anoctamin-5), LGMD2J (titin), LGMD1C (caveolin-3), and EDMD (emerin and lamin A/C) (Level B).

D2. In patients with suspected muscular dystrophy in whom initial genetic testing, muscle biopsy, and dried blood spot test for Pompe disease do not provide a diagnosis, clinicians may obtain genetic consultation or perform parallel sequencing of targeted exomes, whole-exome sequencing, whole-genome screening, or next-generation sequencing to identify the genetic abnormality (Level C).

### **Evaluation and medical management of muscular dystrophies**

In this section we address monitoring and medical management of complications.

***Cardiac involvement.*** *Clinical context.* Our systematic review reveals that many, though not all, muscular dystrophy subtypes have associated cardiac involvement (EVID). Muscular dystrophy patients with cardiac involvement often do not have symptoms such as chest pain, pedal edema, or palpitations that precede cardiac morbidity or sudden cardiac death. Serious cardiac manifestations in patients with muscular dystrophy are often identified only with cardiology testing (PRIN). The detection and appropriate management of cardiac dysfunction are important to reduce morbidity and mortality (PRIN). Patients with muscular dystrophy often have improved quality of life following appropriate pharmacologic treatment, device placement, or surgical intervention for their cardiac involvement (RELA).<sup>e506</sup>

*Recommendations.*

E1. Clinicians should refer newly diagnosed patients with

- a. LGMD1A, LGMD1B, LGMD1D, LGMD1E, LGMD2C–K, LGMD2M–P, BMD, EDMD, and MFM
- b. muscular dystrophy without a specific genetic diagnosis

for cardiology evaluation, including ECG and structural evaluation (echocardiography or cardiac MRI), even if they are asymptomatic from a cardiac standpoint, to guide appropriate management (Level B).

E1a. If ECG or structural cardiac evaluation (e.g., echocardiography) is abnormal, or if the patient has episodes of syncope, near-syncope, or palpitations, clinicians should order rhythm evaluation (e.g., Holter monitor or event monitor) to guide appropriate management (Level B).

E2. Clinicians should refer muscular dystrophy patients with palpitations or who are found to have symptomatic or asymptomatic tachycardia or arrhythmias for cardiology evaluation (Level B).

E3. Clinicians should refer muscular dystrophy patients with signs or symptoms of cardiac failure for cardiology evaluation (e.g., medical management, left ventricular assist device placement, or cardiac transplantation, as deemed necessary by the cardiologist) to prevent cardiac death (Level B).

*Clinical context.* Our systematic review found that muscular dystrophy patients with certain genetic subtypes (LGMD2A, LGMD2B, and LGMD2L) are at very low risk of concomitant

cardiac involvement during the course of their disease (EVID). Asymptomatic patients with these muscular dystrophy subtypes would not benefit from cardiac testing. They would only be exposed to the added risk and costs associated with this testing. The quality of life in asymptomatic muscular dystrophy patients with genetic subtypes at very low risk of concomitant cardiac involvement is not improved by cardiology evaluation and testing (INFER).

*Recommendation.*

E4. It is not obligatory for clinicians to refer patients with LGMD2A, LGMD2B, and LGMD2L for cardiac evaluation unless they develop overt cardiac signs or symptoms (Level B).

*Clinical context.* Our systematic review has demonstrated an important risk of symptomatic involvement of both skeletal muscle and cardiac muscle in female carriers of dystrophinopathy and emerinopathy (EVID). About 15% of carriers of dystrophinopathy have cardiac involvement before 15 years of age. This increases to about 45% in patients above 15 years of age. Similarly, about 18% of female carriers of emerinopathy over the age of 60 years have typical ECG abnormalities (EVID). Carriers of these disorders may not have obvious symptoms of skeletal muscle or cardiac involvement (PRIN). The detection and appropriate management of skeletal muscle weakness and cardiac dysfunction is important in order to reduce morbidity and mortality (PRIN). Patients with muscle weakness and cardiac involvement from other disorders often have improved quality of life following appropriate management and treatment of cardiac dysfunction (RELA).<sup>e507-e509</sup>

*Recommendation.*



E5. Clinicians should encourage female carriers of dystrophinopathy and emerinopathy to seek evaluation by a neuromuscular specialist and a cardiologist to assess for skeletal muscle and cardiac muscle involvement and to proactively treat cardiac involvement (Level B).

***Dysphagia and nutrition.*** *Clinical context.* Patients with muscular dystrophy may have difficulty receiving adequate oral intake due to dysphagia and/or inability to feed themselves due to excessive arm weakness (EVID). Maintaining adequate nutrition and body weight is important for optimizing strength, function, and quality of life (PRIN). When oral intake is inadequate, other means of maintaining intake, such as gastrostomy or jejunostomy feeding tubes, may be needed to maintain optimal nutrition (PRIN). There is evidence from related conditions (ALS) that maintenance of nutrition and body weight prolongs survival (RELA).<sup>e501</sup>

*Recommendation.*

F1. Clinicians should refer muscular dystrophy patients with dysphagia, frequent aspiration, or weight loss for swallowing evaluation and/or gastroenterology evaluation to assess and manage swallowing function and aspiration risk, to teach patients techniques for safe and effective swallowing (e.g., “chin tuck” maneuver, altered food consistencies, etc.), and to consider placement of a gastrostomy/jejunostomy tube for nutritional support (Level B).

**Pulmonary complications.**

*Clinical context.* Our systematic review demonstrates that some forms of muscular dystrophy are associated with oropharyngeal or ventilator muscle weakness and that patients with these forms are at high risk for developing respiratory failure during the course of their disease. Patients with

LGMD2B and LGMD2L rarely, if ever, have symptomatic respiratory involvement from their disease (EVID). Patients with respiratory failure from neuromuscular-related weakness often do not have symptoms, such as dyspnea, that precede the onset of respiratory failure. Impending respiratory failure in these patients is often identified only with pulmonary function tests (PRIN). Respiratory failure constitutes a major source of morbidity, interfering with daytime cognitive function and negatively affecting quality of life (PRIN). In addition, ventilatory and oropharyngeal weakness can threaten survival through the risk of upper airway obstruction and/or bellows failure (RELA).<sup>e501</sup> Patients with respiratory failure secondary to muscle weakness often have improved quality of life with noninvasive pulmonary ventilation (RELA).<sup>e501</sup>

#### *Recommendations.*

G1. Clinicians should order pulmonary function testing (spirometry and maximal inspiratory/expiratory force in the upright and, if normal, supine positions) or refer for pulmonary evaluation (to identify and treat respiratory insufficiency) in muscular dystrophy patients at the time of diagnosis, or if they develop pulmonary symptoms later in their course (Level B).

G1a. In patients with a known high risk of respiratory failure (e.g., those with LGMD2I or MFM), clinicians should obtain periodic pulmonary function testing (spirometry and maximal inspiratory/expiratory force in the upright position and, if normal, in the supine position) or evaluation by a pulmonologist to identify and treat respiratory insufficiency (Level B).

G2. It is not obligatory for clinicians to refer patients with LGMD2B and LGMD2L for pulmonary evaluation or pulmonary function testing unless they are symptomatic (Level C).

G3. Clinicians should refer muscular dystrophy patients with excessive daytime somnolence, nonrestorative sleep (e.g., frequent nocturnal arousals, morning headaches, excessive daytime fatigue), or respiratory insufficiency based on pulmonary function tests for pulmonary or sleep medicine consultation for consideration of noninvasive ventilation to improve quality of life (Level B).

***Cognitive dysfunction and learning disabilities.*** *Clinical context.* Although cognitive dysfunction, reduced IQ, and learning disabilities are not major factors in most patients with limb-girdle muscular dystrophy, they are noted in a few disorders, such as BMD and those disorders that cause a primary or secondary defect in  $\alpha$ -dystroglycan (EVID). Identification and management of these disorders is important to delineate special needs and to provide the resources necessary for these patients to live as normal a life as possible (PRIN).

*Recommendation.*

H1. In muscular dystrophy patients with symptoms suggestive of cognitive dysfunction or learning disabilities, clinicians may order neuropsychological testing, MRI of the brain, and/or developmental pediatrics consultation to assess for and optimally manage CNS involvement (Level C).

**Spinal deformities.** *Clinical context.* Our systematic review has revealed the risk of evolving musculoskeletal spine deformities, such as scoliosis, kyphosis, or rigid spine syndrome, in various muscular dystrophies (EVID). These musculoskeletal deformities can result in discomfort and functional impairment, interfering with gait, activities of daily living, and pulmonary function (PRIN). The proper management of musculoskeletal spine deformities is important in order to reduce discomfort, preserve mobility or ability to sit in a wheelchair, and reduce pulmonary complications (RELA).<sup>e506</sup>

*Recommendations.*

I1. Clinicians should monitor patients with muscular dystrophy for the development of spinal deformities to prevent resultant complications and preserve function (Level B).

I2. Clinicians should refer muscular dystrophy patients with musculoskeletal spine deformities to an orthopedic spine surgeon for monitoring and surgical intervention if it is deemed necessary in order to maintain normal posture, assist mobility, maintain cardiopulmonary function, and optimize quality of life (Level B).

**Osteoporosis.** *Clinical context.* Our systematic review did not provide evidence regarding monitoring for osteoporosis with bone density testing (EVID). However, sedentary lifestyle is one risk factor for osteoporosis (PRIN). Therefore, patients with limb-girdle muscular dystrophy causing limited mobility may be prone to osteoporosis (INFER). They are also prone to falls and therefore may be at a high risk for injuries, including fractures (PRIN). The injuries may in turn further limit mobility (PRIN).

*Recommendation.*

J1. Clinicians may choose to evaluate patients with restricted mobility due to muscular dystrophy with bone density studies for osteoporosis in order to institute timely management and minimize fractures (Level C).

***Infection prophylaxis.*** *Clinical context.* Our systematic review did not provide evidence regarding immunization with pneumococcal vaccination or annual influenza vaccination (EVID). Given the underlying respiratory muscle weakness or spinal deformities in some subtypes of muscular dystrophy, prevention of respiratory infections is important in order to avoid complications, such as respiratory failure, requiring ventilator support (RELA).<sup>e510-e513</sup> The Centers for Disease Control and Prevention (CDC) recommends pneumococcal polysaccharide vaccine (PPSV23) for “all adults aged 65 years and older; adults younger than age 65 years with chronic lung disease (including chronic obstructive pulmonary disease, emphysema, and asthma); chronic cardiovascular diseases; diabetes mellitus; chronic renal failure; nephrotic syndrome; chronic liver disease (including cirrhosis); alcoholism; cochlear implants; cerebrospinal fluid leaks; immunocompromising conditions; and functional or anatomic asplenia;...residents of nursing homes or long-term care facilities; and adults who smoke cigarettes” (PRIN).<sup>e514</sup> Patients with limb-girdle muscular dystrophy may be considered as having a chronic illness, may have cardiorespiratory involvement, and may be residents of long-term care facilities (INFER). Influenza vaccine is recommended annually for all persons over 6 months of age (PRIN).

*Recommendation.*

K1. Clinicians should recommend pneumococcal polysaccharide vaccine (PPSV23) as per the CDC schedule<sup>e514</sup> and annual influenza vaccine to patients with muscular dystrophy in order to prevent respiratory complications of pneumococcal pneumonia and influenza (Level B).

**Rehabilitative management and treatment of muscular dystrophies**

***Clinical rehabilitative management.*** *Clinical context.* Our evidence-based review of the literature on rehabilitative management of muscular dystrophies (LGMD, EDMD, and distal myopathy) consisted primarily of single Class III studies. Thus, the currently available data are not adequate to properly assess the effect of any rehabilitation modality (endurance and strength training, bracing, and assistive devices, including new computer-based technology) (EVID). Large well-designed clinical trials are therefore required to evaluate the role of rehabilitative treatments for these disorders (INFER). However, the principles of the long-term management of patients with these disorders must emphasize maintaining mobility and functional independence for as long as possible, with a focus on maximizing quality of life. The prevention and management of comorbidities, both expected and acquired, is a major part of such management. These comorbidities would include joint contractures, scoliosis, osteoporosis, dysphagia, and restrictive lung disease (expected), as well as obesity, metabolic syndrome, and stress fractures (acquired). Patient-centered, proactive, and collaborative decision making (including all relevant team members) is important, taking into account the patient's wishes and family and social circumstances. An important aspect of ongoing management includes proactively preparing patients with muscular dystrophy and their families for the long-term consequences of muscular dystrophies and engaging in discussions regarding end-of-life care. This helps patients come to

terms with their condition and prepare for the expected complications of their form of muscular dystrophy and avoids the need for hasty decisions made in the throes of a medical crisis (PRIN). There is evidence from studies in other neuromuscular diseases, including ALS, that a multidisciplinary approach is the most effective way to deliver care (RELA).<sup>e515</sup> This model is endorsed by the Muscular Dystrophy Association, which also sponsors these types of clinics. This level of care usually occurs at a tertiary or academic-based medical center, with clinics designed specifically to care for patients with muscular dystrophy and other neuromuscular disorders. The primary clinic team members usually include a neurologist and a physiatrist, along with physical and occupational therapists. Neurogeneticists, pulmonologists, cardiologists, gastroenterologists, orthopedic surgeons, and speech-language pathologists are part of the team. Rehabilitation psychologists, social workers, and vocational rehabilitation counselors can also be valuable members of the team. Once the diagnosis is confirmed, the rehabilitation team, under the direction of a physician (preferably a neuromuscular-trained specialist), can manage clinical problems long-term. Ideally, this would include complete functional assessments using reliable, standardized, reproducible measures in order to quantify a patient's physical and psychosocial performance at any given point in the disease process. This not only helps monitor a patient's overall level of health but also facilitates evaluation for possible enrollment in a clinical trial. With the loss of mobility will come the need for progressively more assistance with activities of daily living, as well as potential medical complications (PRIN). When writing therapy prescriptions, clinicians should be aware of the current allowances from payers for outpatient physical therapy. Patients with muscular dystrophy should see physical and occupational therapists who are experienced in treating these disorders. These therapists often practice in a tertiary care, medical center-based setting (PRIN).

*Recommendations.*

L1. Clinicians should refer patients with muscular dystrophy to a clinic that has access to multiple specialties (e.g., physical therapy, occupational therapy, respiratory therapy, speech and swallowing therapy, cardiology, pulmonology, orthopedics, and genetics) designed specifically to care for patients with muscular dystrophy and other neuromuscular disorders in order to provide efficient and effective long-term care (Level B).

L2. Clinicians might discuss opportunities for participation in clinical trials, if available, with muscular dystrophy patients (Level C).

L3. Clinicians should recommend that patients with muscular dystrophy have periodic assessments by a physical and occupational therapist for symptomatic and preventive screening (Level B).

L4. While respecting and protecting patient autonomy, clinicians should proactively anticipate and facilitate patient and family decision making as the disease progresses, including decisions regarding loss of mobility, need for assistance with activities of daily living, medical complications, and end-of-life care (Level B).

L5. For patients with muscular dystrophy, clinicians should prescribe physical and occupational therapy, as well as bracing and assistive devices that are adapted specifically to the patient's



deficiencies and contractures, in order to preserve mobility and function and prevent contractures (Level B).

***Strength training and aerobic exercise training.*** *Clinical context.* As mentioned earlier, our evidence-based review of the literature on rehabilitation management of muscular dystrophies (LGMD, EDMD, and distal myopathy) consisted primarily of single Class III studies. Thus, the currently available data are not adequate to properly assess the effect of any rehabilitation modality (endurance and strength training, bracing, and assistive devices, including new computer-based technology) (EVID). Despite inadequate research in this area, the available evidence suggests that this population would benefit from both strengthening and aerobic fitness training programs. Due to the muscle degeneration in muscular dystrophy, there may be some risk of exercise-induced muscle damage and subsequent overwork weakness following supramaximal, high-intensity exercise. Overwork weakness is defined as a prolonged decrease in absolute muscle strength and endurance following strenuous or excessive exercise. It is often accompanied by extreme delayed onset muscle soreness, peaking 1–5 days after exercise and possibly inducing myoglobinuria. Clinicians need to be prudent in their recommendations, encouraging alternating periods of physical activity and scheduled rest. Clinicians should also be aware that true overwork weakness has not been demonstrated in any trial of exercise done in this population to date. Future investigations should focus on the primary symptom of fatigue and quantify changes in the ability to work and participate in physical activities as outcome measures of an exercise program. All forms of physical exercise should therefore be prescribed cautiously, using a common sense approach (PRIN). There have been several randomized or quasi-randomized controlled trials comparing strength training programs, aerobic exercise

programs, or both to non-training controls in patients with a variety of neuromuscular disorders (RELA).<sup>e516-e518</sup> On the basis of this literature, both strength training and aerobic exercise programs appear to be safe, without any notable deleterious effects. However, limitations in the design of these trials prevent any conclusions regarding possible benefit (EVID, RELA).

*Recommendations.*

M1. Clinicians may advise patients with muscular dystrophy that aerobic exercise combined with a supervised submaximal strength training program is probably safe (Level C).

M2. Clinicians may advise patients with muscular dystrophy that gentle, low-impact aerobic exercise (swimming, stationary bicycling) improves cardiovascular performance, increases muscle efficiency, and lessens fatigue (Level C).

M3. Clinicians may counsel patients with muscular dystrophy to hydrate adequately, not to exercise to exhaustion, and to avoid supramaximal, high-intensity exercise (Level C).

M4. Clinicians should educate patients with muscular dystrophy who are participating in an exercise program about the warning signs of overwork weakness and myoglobinuria, which include feeling weaker rather than stronger within 30 minutes after exercise, excessive muscle soreness 24–48 hours following exercise, severe muscle cramping, heaviness in the extremities, and prolonged shortness of breath (Level B).

**Medical treatments. Clinical context.** Our systematic review of treatments available for LGMD revealed that adeno-associated virus gene transfer increased the expression of the  $\gamma$ -sarcoglycan and  $\alpha$ -sarcoglycan genes in the injected muscle for 1 and 6 months, respectively<sup>e494,e498,e500</sup> (EVID). These are small proof-of-concept studies. Despite evidence of increased expression of the target protein at the site of injection, effects on the clinical course of the disorder and the long-term side effects of this treatment are yet to be determined (INFER).

Our systematic review found that neutralizing antibody to myostatin (MYO-029) is probably safe and tolerable in patients with BMD and LGMD2A–E and 2I at doses of 1 and 3 mg/kg, although a few serious side effects were noted which require further research. Cutaneous hypersensitivity is noted at 10 and 30 mg/kg doses. There are no data regarding long-term safety. There is probably a trend toward increase in lean body muscle mass, but the study was not powered to assess efficacy<sup>e493</sup> (EVID).

Our systematic review found only one study evaluating the effect of myoblast transplantation<sup>e496</sup> and one study evaluating the effects of subcutaneous growth hormone injections in BMD,<sup>e497</sup> both with inconclusive results.

### *Recommendations.*

N1. Clinicians should not offer patients with LGMD gene therapy outside of a research study designed to determine the efficacy and safety of the treatment (Level R).

N2. Clinicians should not offer patients with LGMD neutralizing antibody to myostatin outside of a research study designed to determine the efficacy and safety of the treatment (Level R).

N3. Clinicians should not offer patients with BMD myoblast transplantation or subcutaneous growth hormone injections outside of a research study designed to determine the efficacy and safety of the treatment (Level R).

## **RECOMMENDATIONS FOR FUTURE RESEARCH**

As the category of LGMDs expands rapidly with advances in molecular diagnostics and new disorders due to specific gene defects are identified, there is need for research in the following areas.

1. Larger prospective, long-term, population-based studies are required to establish the prevalence of these rare disorders, identify the ethnic populations among which they are most prevalent, and evaluate their long-term course, including the incidence of cardiorespiratory complications.
2. Ongoing studies of genotype/phenotype correlation are needed to help establish phenotypic patterns based on genotype and to describe the various phenotypes that are caused by one genotype.
3. The optimal management of cardiorespiratory complications (e.g., frequency and types of screening, effective treatments) should be evaluated.
4. Well-designed studies of the effectiveness of exercise programs, physical therapy, and endurance training are needed.
5. Studies of other treatments should be conducted, including symptomatic treatments such as the effect of orthotics for contractures (nonsurgical/surgical) on mobility and quality of life, as well as specific disease-modifying treatments such as gene therapy and stem cell therapy.

6. Preliminary data suggest that corticosteroids may be effective in  $\alpha$ -dystroglycanopathies.

This finding needs to be replicated in larger, controlled studies.

## **DISCLAIMER**

This statement is provided as an educational service of the American Academy of Neurology and American Association of Neuromuscular & Electrodiagnostic Medicine. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN and AANEM recognize that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. Formal practice recommendations are not intended to replace clinical judgment.

## **CONFLICT OF INTEREST**

The American Academy of Neurology and American Association of Neuromuscular & Electrodiagnostic Medicine are committed to producing independent, critical, and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN and AANEM keep separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN and AANEM limit the participation of authors with substantial conflicts of interest. The AAN and AANEM forbid commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least three AAN committees, at least

one AANEM committee, a network of neurologists, *Neurology* peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at [www.aan.com](http://www.aan.com). For complete information on this process, access the 2004 AAN process manual.<sup>e7</sup>

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**Table e-1. Genetic classification of the limb-girdle and distal muscular dystrophies**

<u>Disease</u>	<u>Inheritance</u>	<u>Chromosome</u>	<u>Affected protein</u>
<b>X-linked muscular dystrophies</b>			
Duchenne/Becker	XR	Xp21	Dystrophin
EDMD-X1	XR	Xq28	Emerin
EDMD-X2/Scapuloperoneal	X-linked	Xq27.2	FHL1
<b>Limb-girdle muscular dystrophies (LGMDs)</b>			
LGMD1A	AD	5q22.3-31.3	Myotilin
LGMD1B	AD	1q11-21	Lamin A/C
LGMD1C	AD	3p25	Caveolin-3
LGMD1D	AD	6q23	DNAJB6
LGMD1E	AD	2q35	Desmin
LGMD1F*	AD	7q32.1-7q32.2	Transportin-3 (TNPO3)
LGMD2A	AR	15q15.1-21.1	Calpain-3
LGMD2B	AR	2p13	Dysferlin
LGMD2C	AR	13q12	$\gamma$ -Sarcoglycan
LGMD2D	AR	17q12-21.3	$\alpha$ -Sarcoglycan
LGMD2E	AR	4q12	$\beta$ -Sarcoglycan
LGMD2F	AR	5q33-34	$\delta$ -Sarcoglycan
LGMD2G	AR	17q11-12	Telethonin

LGMD2H	AR	9q31-33	E3-ubiquitin-ligase (TRIM32)
LGMD2I	AR	19q13	Fukutin-related protein (FKRP)
LGMD2J	AR	2q31	Titin
LGMD2K	AR	9q31	POMT1
LGMD2L	AR	11p14.3	Anoctamin-5
LGMD2M	AR	9q31-33	Fukutin
LGMD2N	AR	14q24	POMT2
LGMD2O	AR	1p32	POMGNT1
LGMD2P	AR	3p21	$\alpha$ -Dystroglycan
LGMD2Q	AR	8q24.3	Plectin
LGMD2R*	AR	2q35	Desmin
LGMD2S*	AR	4q35.1	TRAPPC11

### **Myofibrillar myopathies**

AD	5q22.3-31.3	Myotilin
AD	10q22.3-23.2	ZASP
AD	7q32.1	Filamin C
AD	11q21-23	$\alpha$ B-Crystallin
AD/AR	2q35	Desmin
AR	1p36	Selenoprotein N1
AD	10q25.2-q26.2	BAG3

**Hereditary IBM**

AR-hIBM	AR		GNE
hIBM with FTD and Paget disease	AD		VCP
hIBM3	AD		MYHC-IIA

**Distal dystrophies/myopathies**

Welander	AD	2p13	TIA1
Udd	AD	2q31	Titin
Markesbery-Griggs	AD	10q22.3-23.2	ZASP
Nonaka	AR	9p1-q1	GNE
Miyoshi	AR	2p13	Dysferlin
Laing	AD	14q11	MYH7
Williams	AD	7q32.1	Filamin C
Nebulin myopathy	AR	2q21.2-q22	Nebulin
Early-onset distal myopathy with Kelch-like homologue 9 mutation	AD	9p22	Kelch-like 9

**Other dystrophies**

EDMD3	AD	6q24	Nesprin-1
EDMD4	AD	14q23	Nesprin-2

EDMD5	AD	3p25.1	LUMA
Scapuloperoneal dystrophy	AD	2q35	Desmin
Muscular dystrophy with generalized lipodystrophy	AD	17q21.2	Cavin

Abbreviations: AD = autosomal dominant; AR = autosomal recessive; EDMD = Emery-Dreifuss muscular dystrophy; FTD = frontotemporal dementia; hIBM = hereditary inclusion body myopathy; XR = X-linked recessive.

\*Described after this systematic review was performed and hence not discussed in this guideline.

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**Appendix e-1: Mission statement of GDS**

The mission of the GDS is to prioritize, develop, and publish evidence-based guidelines related to the diagnosis, treatment, and prognosis of neurological disorders.

The GDS is committed to using the most rigorous methods available within our budget, in collaboration with other available AAN resources, to most efficiently accomplish this mission.

**Appendix e-2: 2013–2015 Guideline Development Subcommittee (GDS) members**

Cynthia Harden, MD (Chair); Steven R. Messé, MD, FAAN (Vice-Chair); Richard L. Barbano, MD, PhD, FAAN; Jane Chan, MD, FAAN; Diane Donley, MD; Terry Fife, MD, FAAN; Jeffrey Fletcher, MD; Michael Haboubi, MD; John J. Halperin, MD, FAAN; Cheryl Jaigobin, MD; Andres M. Kanner, MD; Jason Lazarou, MD; David Michelson, MD; Pushpa Narayanaswami, MD, MBBS; Maryam Oskoui, MD; Tamara Pringsheim, MD; Alexander Rae-Grant, MD; Kevin Sheth, MD, FAHA; Kelly Sullivan, PhD; Theresa A. Zesiewicz, MD, FAAN; Jonathan P. Hosey, MD, FAAN (Ex-Officio); Stephen Ashwal, MD, FAAN (Ex-Officio); Deborah Hirtz, MD, FAAN (Ex-Officio); Jacqueline French, MD, FAAN (Ex-Officio)

**Appendix e-3: AANEM Practice Issues Review Panel (PIRP) members**

Yuen T. So, MD, PhD (Co-Chair); Williams S. David, MD, PhD (Co-Chair); Paul E. Barkhaus, MD; Earl J. Craig, MD; Prabhu D. Emmady, MD; Kenneth J. Gaines, MD; James F. Howard, MD; Atul T. Patel, MD; Bharathi Swaminathan, MD; Darrell T. Thomas, MD; Gil I. Wolfe, MD

## Appendix e-4: Complete search strategy

### *Ovid Medline*

1950 to December Week 3 2010 # Searches Results Search Type 1

muscular dystrophies/ and (lbmd\* or (limb adj girdle) or distal or becker or emery or dreifuss or markesberry or griggs or udd or minoka or myoshi or laing or williams or welander).mp.

[mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 1974 Advanced 2

muscular dystrophy, limb girdle/ or ((muscle diseases/ or myopath\*.mp.) and distal.mp.)

[mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 1080 Advanced 3

1 or 2 2829 Advanced 4

exp muscular dystrophies/ 18431 Advanced

5

laminin\*.mp. or lmna protein, human/ or myot protein, human.mp. or calpain.mp. or calpainopath\*.mp. or capn3 protein, human/ or dysferlin\*.mp. or dysf, protein, human/ [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 24315 Advanced

6 exp dystrophin associated proteins/ or sarcoglycan\*.mp. or dystroglycans\*.mp. or telethonin.mp. or tcap protein, human.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 1781 Advanced

7 (trim32\* or fukutin\*).mp. or flkrp protein, human/ or titin.mp. or tcap protein, human.mp. or tcap\*.mp. or pomt\*.mp. or ano5\*.mp. or anoctamin.mp. or pomgnt\*.mp. or desmin.mp. or alpha-crystallin b chain.mp. or ldb3 protein, human.mp. or zasp.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 8612 Advanced

8 (bag3\* or filamin or fhli protein, human or emerin or emd protein, human or resprin\* or myosin heavy chain or myhct or nvl protein, human or matrin 3 or cavin).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 7771 Advanced

9 4 and (5 or 6 or 7 or 8) 1638 Advanced

10 exp muscular dystrophies/ep, ge, cl, bl, pa 10239 Advanced 11

3 and 10 1903 Advanced

12 3 and (exp molecular diagnostic techniques/ or genetic testing.mp. or exp genetic techniques/) [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 1205 Advanced

13 3 and (exp polymerase chain reaction/ or heterozygote detection/ or exp nucleic amplification techniques/ or exp dna probes/ or ("x" adj linked).mp.) [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 617 Advanced

14 9 or 10 or 12 or 13 10712 Advanced

15 14 not case reports/ 8685 Advanced

16 ../ 15 hu=y and yr=1987-2010 5546 Advanced

17 Muscular Dystrophy, Facioscapulohumeral/ 326 Advanced

18 16 not (17 or fascioscap\*.mp.) [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 5364 Advanced

19 3 and 18 1373 Advanced

20 1 or 2 or (exp \*muscular dystrophies/ and 14) 10114 Advanced

21 ../ 20 hu=y and yr=1987-2010 6839 Advanced

22 21 and (creatine kinase/an, bl, du or exp muscles/pa, pp or biops\*.mp. or exp imaging, diagnostic/ or physical examination/) [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 2727 Advanced

23 [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 690821 Advanced

24 exp Cardiovascular Physiological Processes/ 416537 Advanced

25 21 and (23 or 24) 409 Advanced

26 muscle weakness or winging\*).mp. or ambulation/ or quality of life/ or activities of daily living/ or muscular atrophy/ or exp muscles/pa, pp or exp physical therapy modalities/ or muscle strength.mp. or hand strength/ or hand grip/ or grip strength.mp. or exercise\*.mp. or physical endurance/ [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 502739 Advanced

27 21 and 26 2122 Advanced

28 exp Scoliosis/ or exp Braces/ 14674 Advanced

29 (absorptiometry, photon or densitometry\*).mp. or bone density/ or exp bone resorption/ or exp bone disease, metabolic/ [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 109052 Advanced

30 21 and (28 or 29) 44 Advanced

31 exp respiratory insufficiency/ or exp respiratory function tests/ or swallow\*.mp. or dysphagia.mp. or exp vocal disorders/ or polysomnography/ or exp respiration, artificial/ or tracheostomy/ or capnography.mp. or hypercapnia.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 281320 Advanced

32 exp Complementary Therapies/ 142979 Advanced

33 exp Gene Therapy/ 31909 Advanced

34 21 and (31 or 32 or 33) 467 Advanced

35 22 or 25 or 27 or 30 or 34 3421 Advanced

36 limit 35 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial) 348 Advanced

37 35 and ((cohort\* or observation\* or population\* or retrospective\* or prospective\*).mp. or review.pt. or (case adj series).mp. or (case adj controlled).mp.) [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 863 Advanced

38 36 or 37 1134 Advanced

39 limit 38 to yr="1987 - 2012" 266 Advanced



## ***PubMed***

(LGMD\* OR “limb girdle muscular dystrophy” OR distal myopathies[mesh] OR “distal muscular dystrophy” OR “Becker muscular dystrophy” OR “Emery Dreifuss muscular dystrophy” OR “inclusion body myositis” OR “inclusion body myopathy” OR muscular dystrophy, limb girdle[mesh] OR muscular diseases[mesh:noexp] OR muscle weakness[mesh] OR muscular dystrophies[mesh:noexp]) AND (genetics[sh] OR sarcotubular OR dnajb6 OR kelch OR myotilin OR “lamin a/c” OR “caveolin-3” OR “calpain-3” OR dysferlin OR sarcoglycan OR telethonin OR TRIM32 OR FKRP OR Titin OR “o-mannosyltransferase-1” OR POMT\* OR fukutin OR anoctamin OR ANO5 OR “o-mannose- beta 1,2-N-Acetylglucosaminyl transferase” OR POMTGnT1 OR “O-mannosyltransferase-2” OR POMT OR desmin OR “Alpha b Crystallin” OR ZASP OR “Bag-3” OR filamin\* OR FHL1\* OR fhl OR lim domain proteins[mesh] OR emerin OR nesprin OR “Markesbery-Griggs” OR Udd OR Nonaka OR Miyoshi OR Laing OR Williams OR Welander OR “myosin heavy chain” OR “MyHC 7” OR VCP OR “Valosin containing protein” OR “Matrin 3” OR GNE OR epimerase OR Cavin OR selenoprotein OR SEPN1 OR VCPDM OR nebulin OR ”rigid spine” OR dystroglycan OR “transmembrane protein 43” OR tmem\* OR LUMA) NOT muscular dystrophy, duchenne[majr]

## *Cochrane, Embase, Web of Science*

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present # Searches Results Search Type

1 (lgmd\* or "limb girdle muscular dystrophy").mp. or exp distal myopathies/ or "distal muscular dystrophy".mp. or "becker muscular dystrophy".mp. or "emery dreifuss muscular dystrophy".mp. or "inclusion body myositis".mp. or "inclusion body myopathy".mp. or exp muscular dystrophy, limb girdle/ or muscle weakness/ or muscular dystrophy/ or muscular dystrophies/ [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 15307 Advanced

2 1 and ge.fs. 6968 Advanced

3 1 and (sarcotubular or dnajb6 or kelch or myotilin or "lamin a/c" or "caveolin-3" or "calpain-3").mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 498 Advanced

4 1 and (dysferlin or sarcoglycan or telethonin or trim32 or flkrp or titin or "o-mannosyltransferase-1" or pomt\* or fukutin or anoctamin or ano5 or "o-mannose-beta1,2-nacetylglucosaminyltransferase" or pomtgn1).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 921 Advanced

5 1 and ((desmin or "alpha b crystallin" or zasp or "bag-3" or filamin\* of fh11\* or fh1).mp. or exp lim domain proteins/) [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 129 Advanced

6 1 and (emerin or nesprin or "markesbery griggs" or udd or nonaka or miyoshi or laing or williams or welander or "myosin heavy chain" or myhc7 or myhc or vcp or "valosin containing protein" or "matrin 3" or gne or epimerase or cavin or selenoprotein\* or sepn1 or vcpdm or nebulin or "rigid spine" or dystroglycan or "transmembrane protein 43" or tmem\* or luma).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 1182 Advanced

7 2 or 3 or 4 or 5 or 6 7393 Advanced

8 7 not \*muscular dystrophy, duchenne/ 7167 Advanced

9 exp molecular diagnostic techniques/ or "genetic testing".mp. or exp genetic techniques/ or exp polymerase chain reaction/ or heterozygote detection/ or exp nucleic amplications techniques/ or exp dna probes/ or ("x" adj linked).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 1418455 Advanced

10 1 and 9 4060 Advanced

11 7 or 10 7702 Advanced

12 11 not \*muscular dystrophy, duchenne/ 7466 Advanced

13 12 not (muscular dystrophy, fascioscapulohumeral/ or fascioscap\*.mp.) [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 7461 Advanced

14 limit 13 to (english language and humans and yr="1987 - 2012") 4567 Advanced

15 14 and (creatine kinase/an, bl, du or exp muscles/pa, pp or biops\*.mp. or exp imaging, diagnostic/ or physical examination/) [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 1833 Advanced

16 exp heart diseases/di, pa, ep, mo, pp, co or exp heart function tests/ or exp electrocardiography/ or exp echocardiography/ or exp assisted circulation/ or pacemaker, artificial/ or cardiac pacing, artificial.mp. or exp heart transplantation/ 750885 Advanced

17 exp cardiovascular physiological processes/ 446803 Advanced

18 14 and (16 or 17) 211 Advanced

19 (muscle weakness or winging\*).mp. or ambulation/ or quality of life/ or activities of daily living/ or muscular atrophy/ or exp muscles/pa, pp or exp physical therapy modalities/ or muscle strength/ or hand strength/ or hand grip/ or "grip strength".mp. or exercise\*.mp. or physical endurance/ [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 572576 Advanced

20 14 and 19 1405 Advanced

21 exp scoliosis/ or exp braces/ or bone density/ or exp bone resorption/ or absorptiometry, photon/ or densitomet\*.mp. or exp bone diseases, metabolic/ [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 140311 Advanced

22 14 and 21 40 Advanced

23 exp respiratory insufficiency/ or exp respiratory function tests/ or swallow\*.mp. or dysphagia.mp. or exp vocal disorders/ or polysomnography/ or exp respiration, artificial/ or tracheostomy/ or capnography.mp. or hypercapn\*.mp. or exp deglutition disorders/ [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 332065 Advanced

24 14 and 23 83 Advanced

25 14 and (exp complementary therapies/ or exp gene therapy/) 185 Advanced

26 15 or 18 or 20 or 22 or 24 or 25 2235 Advanced

## *Updated Ovid Medline*

1950 to December Week 3 2010 # Searches Results Search Type 1

muscular dystrophies/ and (lbmd\* or (limb adj girdle) or distal or becker or emery or dreifuss or markesberry or griggs or udd or minoka or myoshi or laing or williams or welander).mp.

[mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 1974 Advanced 2

muscular dystrophy, limb girdle/ or ((muscle diseases/ or myopath\*.mp.) and distal.mp.)

[mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 1080 Advanced 3

1 or 2 2829 Advanced 4

exp muscular dystrophies/ 18431 Advanced 5

laminin\*.mp. or lmna protein, human/ or myot protein, human.mp. or calpain.mp. or calpainopath\*.mp. or capn3 protein, human/ or dysferlin\*.mp. or dysf, protein, human/ [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 24315 Advanced 6

exp dystrophin associated proteins/ or sarcoglycan\*.mp. or dystroglycans\*.mp. or telethonin.mp. or tcap protein, human.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 1781 Advanced 7

(trim32\* or fukutin\*).mp. or flkrp protein, human/ or titin.mp. or tcap protein, human.mp. or tcap\*.mp. or pomt\*.mp. or ano5\*.mp. or anoctamin.mp. or pomgnt\*.mp. or desmin.mp. or alpha-crystallin b chain.mp. or ldb3 protein, human.mp. or zasp.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 8612 Advanced 8

(bag3\* or filamin or fhli protein, human or emerlin or emd protein, human or resprin\* or myosin heavy chain or myhct or nvl protein, human or matrin 3 or cavin).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 7771 Advanced 9

4 and (5 or 6 or 7 or 8) 1638 Advanced 10

exp muscular dystrophies/ep, ge, cl, bl, pa 10239 Advanced 11

3 and 10 1903 Advanced 12

3 and (exp molecular diagnostic techniques/ or genetic testing.mp. or exp genetic techniques/) [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 1205 Advanced 13

3 and (exp polymerase chain reaction/ or heterozygote detection/ or exp nucleic amplification techniques/ or exp dna probes/ or ("x" adj linked).mp.) [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 617 Advanced 14

9 or 10 or 12 or 13 10712 Advanced 15

14 not case reports/ 8685 Advanced 16

..l/ 15 hu=y and yr=1987-2010 5546 Advanced 17

Muscular Dystrophy, Facioscapulohumeral/ 326 Advanced 18

16 not (17 or fascioscap\*.mp.) [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 5364 Advanced 19

3 and 18 1373 Advanced 20

1 or 2 or (exp \*muscular dystrophies/ and 14) 10114 Advanced 21

..l/ 20 hu=y and yr=1987-2010 6839 Advanced 22

21 and (creatine kinase/an, bl, du or exp muscles/pa, pp or biops\*.mp. or exp imaging,

diagnostic/ or physical examination/) [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 2727 Advanced 23  
 exp heart diseases/di, pa, ep, mo, pp, co or exp heart function tests/ or exp electrocardiography/ or exp echocardiography/ or exp assisted circulation/ or pacemaker, artificial/ or cardiac pacing, artificial.mp. or exp heart transplantation/ [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 690821 Advanced 24  
 exp Cardiovascular Physiological Processes/ 416537 Advanced 25  
 21 and (23 or 24) 409 Advanced 26  
 (muscle weakness or winging\*).mp. or ambulation/ or quality of life/ or activities of daily living/ or muscular atrophy/ or exp muscles/pa, pp or exp physical therapy modalities/ or muscle strength.mp. or hand strength/ or hand grip/ or grip strenth.mp. or exercise\*.mp. or physical endurance/ [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 502739 Advanced 27  
 21 and 26 2122 Advanced 28  
 exp Scoliosis/ or exp Braces/ 14674 Advanced 29  
 (absorptiometry, photon or densitometry\*).mp. or bone density/ or exp bone resorption/ or exp bone disease, metabolic/ [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 109052 Advanced 30  
 21 and (28 or 29) 44 Advanced 31  
 exp respiratory insufficiency/ or exp respiratory function tests/ or swallow\*.mp. or dysphagia.mp. or exp vocal disorders/ or polysomnography/ or exp respiration, artificial/ or tracheostomy/ or capnography.mp. or hypercapnia.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 281320 Advanced 32  
 exp Complementary Therapies/ 142979 Advanced 33  
 exp Gene Therapy/ 31909 Advanced 34  
 21 and (31 or 32 or 33) 467 Advanced 35  
 22 or 25 or 27 or 30 or 34 3421 Advanced 36  
 limit 35 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial) 348 Advanced 37  
 35 and ((cohort\* or observation\* or population\* or retrospective\* or prospective\*).mp. or review.pt. or (case adj series).mp. or (case adj controlled).mp.) [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 863 Advanced 38  
 36 or 37 1134 Advanced 39  
 limit 38 to yr="1987 - 1995" 266 Advanced

## **Appendix e-5: Classification of Evidence Schemes**

### **Screening**

*Class I:* A statistical, population-based sample of patients studied at a uniform point in time (usually early) during the course of the condition. All patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation that is masked to the patients' clinical presentations.

*Class II:* A statistical, non-referral-clinic-based sample of patients studied at a uniform point in time (usually early) during the course of the condition. Most patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation that is masked to the patients' clinical presentations.

*Class III:* A sample of patients studied during the course of the condition. Some patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation by someone other than the treating physician.

*Class IV:* Studies not meeting Class I, II or III criteria including consensus, expert opinion or a case report

### **Therapy**

*Class I:* Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required:

- a) Concealed allocation
- b) primary outcome(s) clearly defined
- c) exclusion/inclusion criteria clearly defined

- d) adequate accounting for drop-outs and cross-overs with numbers sufficiently low to have minimal potential for bias
- e) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

*Class II:* Prospective matched group cohort study in a representative population with masked outcome assessment that meets a-e above OR a RCT in a representative population that lacks one criteria a-d.

*Class III:* All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.

*Class IV:* Evidence from uncontrolled studies, case series, case reports, or expert opinion.

## Appendix e-6: Clinical Contextual Profiles Determining Levels of Obligation for Recommendations

### Diagnosis of Muscular Dystrophies

A00. Clinicians should refer patients with suspected muscular dystrophy to neuromuscular centers to optimize the diagnostic evaluation and subsequent management (Level B).

Strength of Recommendation										
Modifier		R/U		C		B		A		Consensus
Availability		Limited	0	Sometimes	1	Usually	2	Universal	5	No
Financial burden		Prohibitive	0	Moderate	0	Minimal	5	None	3	Yes
Variation in preferences		Large	0	Moderate	0	Small	3	Minimal	5	Yes
Importance of outcomes		Not important	0	Somewhat Imp	1	Very Imp	6	Critical	1	Yes
Benefit relative to Harm		Too Close	0	Modest	1	Moderate	4	Large	3	No

Strength of Inference					
Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	x	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

A0. For patients with suspected muscular dystrophy, clinicians should use a clinical approach to diagnosis based on the clinical phenotype, including the pattern of muscle involvement, inheritance pattern, age at onset, and associated manifestations (e.g., early contractures, cardiac or respiratory involvement) (Level B).

Strength of Recommendation										
Modifier		R/U		C		B		A		Consensus
Availability		Limited	0	Sometimes	1	Usually	2	Universal	5	No
Financial burden		Prohibitive	0	Moderate	0	Minimal	5	None	3	Yes
Variation in preferences		Large	0	Moderate	0	Small	3	Minimal	5	Yes
Importance of outcomes		Not important	0	Somewhat Imp	1	Very Imp	6	Critical	1	Yes
Benefit relative to Harm		Too Close	0	Modest	1	Moderate	4	Large	3	No

Strength of Inference					
Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	x	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes



*Limb-girdle pattern of weakness (figures 3 to 5).*

A1. In patients with limb-girdle weakness and suspected muscular dystrophy with probable autosomal dominant inheritance, cardiomyopathy, respiratory involvement, EMG with myotonic or “pseudomyotonic” discharges (the latter characterized by runs of decrescendo positive sharp wave discharges without the typical waxing and waning in amplitude and frequency seen in myotonic discharges), ankle dorsiflexor weakness (foot drop), and muscle biopsy (if performed) showing features of myofibrillar myopathy, clinicians should perform genetic testing for mutations in the genes for desmin (LGMD1E), myotilin (LGMD1A), DNAJB6 (LGMD1D), ZASP, filamin C,  $\alpha$ B-crystallin, and titin (Level B).

Strength of Recommendation										
Modifier		R/U	C		B		A		Consensus	
Availability		Limited	0	Sometimes	3	Usually	4	Universal	1	No
Financial burden		Prohibitive	0	Moderate	4	Minimal	4	None	0	Yes
Variation in preferences		Large	0	Moderate	2	Small	3	Minimal	3	No
Importance of outcomes		Not important	0	Somewhat Imp	1	Very Imp	6	Critical	1	Yes
Benefit relative to Harm		Too Close	0	Modest	0	Moderate	4	Large	4	Yes

Strength of Inference						
Element	Weak	Modest		Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%		≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%		≥80% to 100%	x	Yes
Acceptance of Principles	<50%	≥50% to < 80%		≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%		≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low		Moderate	High	Yes

There was substantial consensus after round 2. Based on the modifiers (availability, financial burden, variations), the panel selected Level B using informal consensus.

A2. In patients with limb-girdle weakness and suspected muscular dystrophy with probable autosomal dominant inheritance, rippling muscles, and percussion-induced rapid contractions, clinicians should perform genetic testing for mutations in the caveolin-3 gene (LGMD1C) (Level B).

Strength of Recommendation										
Modifier		R/U	C		B		A		Consensus	
Availability		Limited	0	Sometimes	1	Usually	6	Universal	1	Yes
Financial burden		Prohibitive	0	Moderate	2	Minimal	6	None	0	Yes
Variation in preferences		Large	0	Moderate	3	Small	1	Minimal	4	No
Importance of outcomes		Not important	0	Somewhat Imp	4	Very Imp	4	Critical	0	Yes
Benefit relative to Harm		Too Close	0	Modest	0	Moderate	7	Large	1	Yes

Strength of Inference					
Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

There was substantial consensus after round 2. Based on the modifiers (availability, financial burden, variations), the panel selected Level B using informal consensus.

A3. In patients with limb-girdle weakness and suspected muscular dystrophy with probable autosomal dominant inheritance, early humeroperoneal weakness, contractures (neck, elbows, knee, ankle), and cardiomyopathy, clinicians should perform genetic testing for mutations in the lamin A/C gene (LGMD1B or AD-EDMD) (Level B).

Strength of Recommendation									
Modifier	R/U		C		B		A	Consensus	
Availability	Limited	0	Sometimes	0	Usually	7	Universal	1	Yes
Financial burden	Prohibitive	0	Moderate	0	Minimal	5	None	3	Yes
Variation in preferences	Large	0	Moderate	1	Small	0	Minimal	7	Yes
Importance of outcomes	Not important	0	Somewhat Imp	0	Very Imp	4	Critical	4	Yes
Benefit relative to Harm	Too Close	0	Modest	0	Moderate	2	Large	6	Yes

Strength of Inference					
Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	x	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

A4. In patients with limb-girdle weakness and suspected muscular dystrophy with probable autosomal dominant inheritance, distal weakness, myotonic discharges on EMG, past or family history of Paget disease, frontotemporal dementia, or motor neuron disease, clinicians should perform genetic testing for mutations in *VCP* (hBMPFD) (Level B).

Strength of Recommendation									
Modifier	R/U		C		B	A	Consensus		
Availability	Limited	0	Sometimes	2	Usually	5	Universal	1	No
Financial burden	Prohibitive	0	Moderate	2	Minimal	6	None	0	Yes
Variation in preferences	Large	0	Moderate	3	Small	2	Minimal	3	No
Importance of outcomes	Not important	1	Somewhat Imp	3	Very Imp	4	Critical	0	No
Benefit relative to Harm	Too Close	0	Modest	3	Moderate	5	Large	0	Yes

Strength of Inference						
Element	Weak		Modest	Moderate	Strong	Consensus
Internal inferences	<50%		≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%		≥50% to < 80%	≥80% to 100%	x	Yes
Acceptance of Principles	<50%		≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%		≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low		Low	Moderate	High	Yes

There was substantial consensus after round 2. Based on the modifiers (availability, financial burden, variations), the panel selected Level B using informal consensus.

A5. In patients with limb-girdle weakness and suspected muscular dystrophy who either do not have clinical features to suggest a specific form of dystrophy or in whom initial genetic testing is not informative, clinicians should perform muscle biopsy in order to delineate characteristic features that direct further genetic testing (such as immunohistochemistry/immunoblotting for various sarcolemmal proteins, calpain-3, or features of myofibrillar myopathy; see figures 4 and 5) or to exclude an alternative diagnosis (e.g., a metabolic myopathy, mitochondrial myopathy, congenital myopathy, or inflammatory myopathy) (Level B).

Strength of Recommendation										
Modifier		R/U	C	B	A	Consensus				
Availability		Limited	0	Sometimes 2	Usually 4	Universal 2	No			
Financial burden		Prohibitive	0	Moderate 0	Minimal 6	None 2	Yes			
Variation in preferences		Large	0	Moderate 2	Small 4	Minimal 2	No			
Importance of outcomes		Not important	0	Somewhat Imp 0	Very Imp 6	Critical 2	Yes			
Benefit relative to Harm		Too Close	0	Modest 0	Moderate 6	Large 2	Yes			

Strength of Inference					
Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	x	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

A6. In patients with limb-girdle weakness and suspected muscular dystrophy with probable autosomal recessive inheritance, scapular winging but no calf hypertrophy, and normal cardiorespiratory function, clinicians should perform initial genetic testing for mutations in calpain-3 (LGMD2A). Patients of English, French, Spanish, Italian, Portuguese, or Brazilian descent may have a higher pretest probability of this disorder (Level B).

Strength of Recommendation									
Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	1	Usually	6	Universal	1	Yes
Financial burden	Prohibitive	0	Moderate	2	Minimal	5	None	1	No
Variation in preferences	Large	0	Moderate	2	Small	2	Minimal	4	No
Importance of outcomes	Not important	1	Somewhat Imp	4	Very Imp	3	Critical	0	No
Benefit relative to Harm	Too Close	0	Modest	3	Moderate	5	Large	0	Yes

  

Strength of Inference					
Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

There was substantial consensus after round 2. Based on the modifiers (availability, financial burden, variations), the panel selected Level B using informal consensus.

A7. In patients with limb-girdle weakness and suspected muscular dystrophy with probable autosomal recessive inheritance and calf atrophy and weakness (i.e., inability to stand on toes), clinicians should perform genetic testing for mutations in anoctamin-5 (LGMD2L) or dysferlin (LGMD2B). If the onset of symptoms is in the teens or early 20s or the patient is from Asia, clinicians should assess for dysferlin mutations first and, if negative, test for anoctamin-5 mutations. If the onset of symptoms is in the 30s or later or the patient is of English or northern European ancestry, clinicians should assess for anoctamin-5 mutations first and, if negative, test for dysferlin mutations (Level B).

Strength of Recommendation							
Modifier	R/U		C	B	A		Consensus
Availability	Limited	0	Sometimes 2	Usually 5	Universal 1		No
Financial burden	Prohibitive	0	Moderate 2	Minimal 6	None 0		Yes
Variation in preferences	Large	0	Moderate 2	Small 2	Minimal 4		No
Importance of outcomes	Not important	1	Somewhat Imp 3	Very Imp 4	Critical 0		No
Benefit relative to Harm	Too Close	0	Modest 3	Moderate 5	Large 0		Yes

  

Strength of Inference							
Element	Weak		Modest	Moderate	Strong		Consensus
Internal inferences	<50%		≥50% to < 80%	≥80% to < 100%	100%		Yes
Strong related evidence	<50%		≥50% to < 80%	≥80% to 100%	X		Yes
Acceptance of Principles	<50%		≥50% to < 80%	≥80% to < 100%	100%		Yes
Logical	<50%		≥50% to < 80%	≥ 80% to < 100%	100%		Yes
Confidence in Evidence	Very Low		Low	Moderate	High		Yes

There was substantial consensus after round 2. Based on the modifiers (availability, financial burden, variations), the panel selected Level B using informal consensus.

A8. In patients with limb-girdle weakness and suspected muscular dystrophy with probable autosomal recessive inheritance and muscle biopsy immunohistochemistry showing reduction in  $\alpha$ -,  $\beta$ -,  $\gamma$ -, or  $\delta$ -sarcoglycans, clinicians should perform genetic testing for mutations in the sarcoglycan genes (LGMD2C–2F) (Level B).

Strength of Recommendation							
Modifier	R/U		C	B	A		Consensus
Availability	Limited	0	Sometimes 1	Usually 7	Universal 0		Yes
Financial burden	Prohibitive	0	Moderate 1	Minimal 7	None 0		Yes
Variation in preferences	Large	0	Moderate 1	Small 6	Minimal 1		Yes
Importance of outcomes	Not important	0	Somewhat Imp 2	Very Imp 6	Critical 0		Yes
Benefit relative to Harm	Too Close	0	Modest 0	Moderate 7	Large 1		Yes

  

Strength of Inference							
Element	Weak		Modest	Moderate	Strong		Consensus
Internal inferences	<50%		≥50% to < 80%	≥80% to < 100%	100%		Yes
Strong related evidence	<50%		≥50% to < 80%	≥80% to 100%	X		Yes
Acceptance of Principles	<50%		≥50% to < 80%	≥80% to < 100%	100%		Yes
Logical	<50%		≥50% to < 80%	≥ 80% to < 100%	100%		Yes
Confidence in Evidence	Very Low		Low	Moderate	High		Yes

A9. In patients with limb-girdle weakness and suspected muscular dystrophy with probable autosomal recessive inheritance who are of Hutterite descent, clinicians should perform genetic testing for mutations in *TRIM32* (LGMD2H) (Level B).

Strength of Recommendation						
Modifier	R/U		C	B	A	Consensus
Availability	Limited	0	Sometimes 4	Usually 3	Universal 1	No
Financial burden	Prohibitive	0	Moderate 2	Minimal 6	None 0	Yes
Variation in preferences	Large	0	Moderate 2	Small 4	Minimal 2	No
Importance of outcomes	Not important	1	Somewhat Imp 4	Very Imp 3	Critical 0	No
Benefit relative to Harm	Too Close	0	Modest 3	Moderate 5	Large 0	Yes

  

Strength of Inference					
Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

There was substantial consensus after round 2. Based on the modifiers (availability, financial burden, variations), the panel selected Level B using informal consensus.

A10. In patients with limb-girdle weakness and suspected muscular dystrophy with probable autosomal recessive inheritance, scapular winging, calf hypertrophy, and early cardiorespiratory involvement, clinicians should perform initial genetic testing for mutations in *FKRP* (LGMD2I). Patients of northern European descent may have a higher pretest probability of this disorder (Level B).

Strength of Recommendation						
Modifier	R/U		C	B	A	Consensus
Availability	Limited	0	Sometimes 1	Usually 6	Universal 1	Yes
Financial burden	Prohibitive	0	Moderate 1	Minimal 7	None 0	Yes
Variation in preferences	Large	0	Moderate 0	Small 4	Minimal 4	Yes
Importance of outcomes	Not important	1	Somewhat Imp 0	Very Imp 6	Critical 1	Yes
Benefit relative to Harm	Too Close	0	Modest 1	Moderate 4	Large 3	No

  

Strength of Inference					
Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

A11. In patients with limb-girdle weakness and suspected muscular dystrophy with probable autosomal recessive inheritance and mental retardation, clinicians should screen for mutations in

genes that cause primary or secondary deficiency of  $\alpha$ -dystroglycan (LGMD2K, LGMD2M, LGMD2N, LGMD2O, and LGMD2P) (Level B).

Strength of Recommendation									
Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	3	Usually	4	Universal	1	No
Financial burden	Prohibitive	0	Moderate	5	Minimal	3	None	0	Yes
Variation in preferences	Large	0	Moderate	3	Small	5	Minimal	0	Yes
Importance of outcomes	Not important	1	Somewhat Imp	1	Very Imp	6	Critical	0	No
Benefit relative to Harm	Too Close	0	Modest	2	Moderate	6	Large	0	Yes

  

Strength of Inference					
Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	$\geq 50\%$ to < 80%	$\geq 80\%$ to < 100%	100%	Yes
Strong related evidence	<50%	$\geq 50\%$ to < 80%	$\geq 80\%$ to 100%	X	Yes
Acceptance of Principles	<50%	$\geq 50\%$ to < 80%	$\geq 80\%$ to < 100%	100%	Yes
Logical	<50%	$\geq 50\%$ to < 80%	$\geq 80\%$ to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

There was substantial consensus after round 2. Based on the modifiers (availability, financial burden, variations), the panel selected Level B using informal consensus.

A12. In patients with limb-girdle weakness and suspected muscular dystrophy with probable autosomal recessive inheritance and epidermolysis bullosa or pyloric atresia, clinicians should perform genetic testing for mutations in plectin (Level B).

Strength of Recommendation									
Modifier	R/U		C		B		A		Consensus
Availability	Limited	1	Sometimes	5	Usually	2	Universal	0	No
Financial burden	Prohibitive	0	Moderate	3	Minimal	5	None	0	Yes
Variation in preferences	Large	0	Moderate	3	Small	4	Minimal	1	No
Importance of outcomes	Not important	2	Somewhat Imp	3	Very Imp	3	Critical	0	No
Benefit relative to Harm	Too Close	0	Modest	3	Moderate	5	Large	0	Yes

  

Strength of Inference					
Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	$\geq 50\%$ to < 80%	$\geq 80\%$ to < 100%	100%	Yes
Strong related evidence	<50%	$\geq 50\%$ to < 80%	$\geq 80\%$ to 100%	X	Yes
Acceptance of Principles	<50%	$\geq 50\%$ to < 80%	$\geq 80\%$ to < 100%	100%	Yes
Logical	<50%	$\geq 50\%$ to < 80%	$\geq 80\%$ to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

There was substantial consensus after round 2. Based on the modifiers (availability, financial burden, variations), the panel selected Level B using informal consensus.

A13. In male patients with limb-girdle weakness and suspected muscular dystrophy with probable X-linked inheritance, clinicians should perform genetic testing for mutations in the dystrophin gene (Duchenne or Becker muscular dystrophy) (Level B).

Strength of Recommendation									
Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	0	Usually	6	Universal	2	Yes
Financial burden	Prohibitive	0	Moderate	0	Minimal	6	None	2	Yes
Variation in preferences	Large	0	Moderate	0	Small	1	Minimal	7	Yes
Importance of outcomes	Not important	0	Somewhat Imp	0	Very Imp	4	Critical	4	Yes
Benefit relative to Harm	Too Close	0	Modest	0	Moderate	2	Large	6	Yes

Strength of Inference									
Element	Weak		Modest		Moderate		Strong		Consensus
Internal inferences	<50%		≥50% to < 80%		≥80% to < 100%		100%		Yes
Strong related evidence	<50%		≥50% to < 80%		≥80% to 100%		X		Yes
Acceptance of Principles	<50%		≥50% to < 80%		≥80% to < 100%		100%		Yes
Logical	<50%		≥50% to < 80%		≥ 80% to < 100%		100%		Yes
Confidence in Evidence	Very Low		Low		Moderate		High		Yes

A14. In patients with limb-girdle weakness and suspected muscular dystrophy with probable autosomal recessive inheritance and no other specific clinical features or in whom muscle biopsy does not inform genetic testing, clinicians should perform dried blood spot test for  $\alpha$ -glucosidase (acid maltase) deficiency or Pompe disease (Level B).

Strength of Recommendation										
Modifier		R/U	C		B		A		Consensus	
Availability		Limited	0	Sometimes	0	Usually	6	Universal	2	Yes
Financial burden		Prohibitive	0	Moderate	0	Minimal	4	None	4	Yes
Variation in preferences		Large	0	Moderate	0	Small	4	Minimal	4	Yes
Importance of outcomes		Not important	0	Somewhat Imp	2	Very Imp	3	Critical	3	No
Benefit relative to Harm		Too Close	0	Modest	0	Moderate	4	Large	4	Yes

Strength of Inference									
Element		Weak	Modest		Moderate		Strong		Consensus
Internal inferences		<50%	≥50% to < 80%		≥80% to < 100%		100%		Yes
Strong related evidence		<50%	≥50% to < 80%		≥80% to 100%		x		Yes
Acceptance of Principles		<50%	≥50% to < 80%		≥80% to < 100%		100%		Yes
Logical		<50%	≥50% to < 80%		≥ 80% to < 100%		100%		Yes
Confidence in Evidence		Very Low	Low		Moderate		High		Yes

A15. In female patients with limb-girdle weakness and suspected muscular dystrophy with probable X-linked inheritance, clinicians should perform genetic testing for dystrophin mutations or perform a muscle biopsy and immunostain for dystrophin to assess for a mosaic pattern of staining. If abnormal immunostaining is present, clinicians should confirm the diagnosis of



manifesting carrier of dystrophinopathy with genetic testing for mutations in the dystrophin gene (Level B).

Strength of Recommendation										
Modifier		R/U	C		B		A		Consensus	
Availability		Limited	0	Sometimes	2	Usually	3	Universal	3	No
Financial burden		Prohibitive	0	Moderate	2	Minimal	5	None	1	No
Variation in preferences		Large	0	Moderate	2	Small	4	Minimal	2	No
Importance of outcomes		Not important	0	Somewhat Imp	1	Very Imp	4	Critical	3	No
Benefit relative to Harm		Too Close	0	Modest	0	Moderate	6	Large	2	Yes

Strength of Inference						
Element	Weak	Modest		Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%		≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%		≥80% to 100%	X	Yes
Acceptance of Principles	<50%	≥50% to < 80%		≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%		≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low		Moderate	High	Yes

There was substantial consensus after round 2. Based on the modifiers (availability, financial burden, variations), the panel selected Level B using informal consensus.

### *Humero-peroneal weakness (figure e-1).*

B1. In patients with humero-peroneal weakness and suspected muscular dystrophy with probable autosomal dominant inheritance, early cardiac involvement, and no joint laxity, clinicians should perform genetic testing for mutations in the lamin A/C gene (AD-EDMD, LGMD1B). If the inheritance pattern is probably X-linked, clinicians should perform genetic testing for mutations in the emerin gene (XR-EDMD) (Level B).

Strength of Recommendation										
Modifier		R/U		C		B		A		Consensus
Availability		Limited	0	Sometimes	1	Usually	5	Universal	2	No
Financial burden		Prohibitive	0	Moderate	1	Minimal	4	None	3	No
Variation in preferences		Large	0	Moderate	2	Small	0	Minimal	6	No
Importance of outcomes		Not important	0	Somewhat Imp	2	Very Imp	2	Critical	4	No
Benefit relative to Harm		Too Close	0	Modest	1	Moderate	2	Large	5	Yes

Strength of Inference					
Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	x	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

There was substantial consensus after round 2. Based on the modifiers (availability, financial burden, variations), the panel selected Level B using informal consensus.

B2. In patients with humeroperoneal weakness and suspected muscular dystrophy with early cardiac involvement and no joint laxity who do not possess mutations in the lamin A/C or emerin gene, clinicians should perform muscle biopsy to delineate characteristic abnormalities that direct further genetic testing (see figure e-1 for muscle biopsy features that direct genetic testing) (Level B).

Strength of Recommendation									
Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	2	Usually	6	Universal	0	Yes
Financial burden	Prohibitive	0	Moderate	1	Minimal	7	None	0	Yes
Variation in preferences	Large	0	Moderate	0	Small	7	Minimal	1	Yes
Importance of outcomes	Not important	1	Somewhat Imp	1	Very Imp	4	Critical	2	No
Benefit relative to Harm	Too Close	0	Modest	1	Moderate	6	Large	1	Yes

  

Strength of Inference					
Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

B3. In patients with humeroperoneal weakness and suspected muscular dystrophy with probable autosomal dominant inheritance, joint laxity, protuberant calcaneus, and no cardiac involvement, clinicians should perform genetic testing for mutations in the collagen VI gene (Bethlem myopathy). If the inheritance pattern is probably autosomal recessive with congenital onset, clinicians should perform genetic testing for mutations in the collagen VI gene (Ullrich myopathy) (Level B).

Strength of Recommendation						
Modifier	R/U		C	B	A	Consensus
Availability	Limited	0	Sometimes 1	Usually 6	Universal 1	Yes
Financial burden	Prohibitive	0	Moderate 3	Minimal 5	None 0	Yes
Variation in preferences	Large	0	Moderate 2	Small 1	Minimal 5	No
Importance of outcomes	Not important	1	Somewhat Imp 3	Very Imp 4	Critical 0	No
Benefit relative to Harm	Too Close	0	Modest 3	Moderate 5	Large 0	Yes

  

Strength of Inference					
Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

There was substantial consensus after round 2. Based on the modifiers (availability, financial burden, variations), the panel selected Level B using informal consensus.

### *Distal muscular dystrophy.*

C1. In patients with late adult onset of index finger and wrist extensor weakness followed by atrophy and weakness of hand muscles and muscle biopsy showing rimmed vacuoles, clinicians should make a diagnosis of Welander distal myopathy. Patients of Swedish or Finnish descent may have a higher pretest probability of this disorder. Clinicians should confirm the diagnosis with genetic testing for Welander myopathy when testing becomes commercially available (Level B).

Strength of Recommendation						
Modifier	R/U		C	B	A	Consensus
Availability	Limited	3	Sometimes 1	Usually 1	Universal 3	No
Financial burden	Prohibitive	0	Moderate 2	Minimal 4	None 2	No
Variation in preferences	Large	0	Moderate 5	Small 0	Minimal 3	No
Importance of outcomes	Not important	2	Somewhat Imp 3	Very Imp 3	Critical 0	No
Benefit relative to Harm	Too Close	0	Modest 3	Moderate 5	Large 0	Yes

  

Strength of Inference					
Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

There was substantial consensus after round 2. Based on the modifiers (availability, financial burden, variations), the panel selected Level B using informal consensus.

C2. In patients with suspected distal muscular dystrophy and probable autosomal recessive inheritance with early onset of calf weakness, clinicians should perform genetic testing for mutations in the anoctamin-5 and dysferlin genes. If the patient is of northern European descent, clinicians should perform initial genetic testing for mutations in the anoctamin-5 gene (LGMD2L) and, if negative, perform genetic testing for mutations in the dysferlin gene (LGMD2B). If the patient is from eastern Asia (Japan, China, Korea), clinicians should perform initial genetic testing for mutations in the dysferlin gene (LGMD2B, Miyoshi myopathy) and, if negative, perform genetic testing for mutations in the anoctamin-5 gene (LGMD2L) (Level B).

Strength of Recommendation									
Modifier	R/U		C		B		A	Consensus	
Availability	Limited	0	Sometimes	4	Usually	3	Universal	1	No
Financial burden	Prohibitive	0	Moderate	3	Minimal	5	None	0	Yes
Variation in preferences	Large	0	Moderate	3	Small	5	Minimal	0	Yes
Importance of outcomes	Not important	1	Somewhat Imp	3	Very Imp	4	Critical	0	No
Benefit relative to Harm	Too Close	0	Modest	3	Moderate	5	Large	0	Yes

  

Strength of Inference					
Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

There was substantial consensus after round 2. Based on the modifiers (availability, financial burden, variations), the panel selected Level B using informal consensus.

C3. In patients with suspected distal muscular dystrophy and probable autosomal recessive inheritance with early onset (<30 years of age) of progressive foot drop who are of Japanese or Middle Eastern Jewish descent, clinicians should perform initial genetic testing for *GNE* mutations (AR-hIBM) (Level B).

Strength of Recommendation						
Modifier	R/U		C	B	A	Consensus
Availability	Limited	0	Sometimes 4	Usually 3	Universal 1	No
Financial burden	Prohibitive	0	Moderate 2	Minimal 6	None 0	Yes
Variation in preferences	Large	0	Moderate 3	Small 2	Minimal 3	No
Importance of outcomes	Not important	1	Somewhat Imp 3	Very Imp 4	Critical 0	No
Benefit relative to Harm	Too Close	0	Modest 3	Moderate 5	Large 0	Yes

  

Strength of Inference					
Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

There was substantial consensus after round 2. Based on the modifiers (availability, financial burden, variations), the panel selected Level B using informal consensus.

C4. In patients with suspected distal muscular dystrophy without the clinical features in C2 or C3 above, clinicians should perform a muscle biopsy to direct further genetic testing (see figure e-2 for biopsy and clinical features that direct genetic testing) (Level B).

Strength of Recommendation						
Modifier	R/U		C	B	A	Consensus
Availability	Limited	0	Sometimes 2	Usually 6	Universal 0	Yes
Financial burden	Prohibitive	0	Moderate 3	Minimal 5	None 0	Yes
Variation in preferences	Large	0	Moderate 0	Small 7	Minimal 1	Yes
Importance of outcomes	Not important	1	Somewhat Imp 0	Very Imp 7	Critical 0	Yes
Benefit relative to Harm	Too Close	0	Modest 1	Moderate 6	Large 1	Yes

  

Strength of Inference					
Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

*Other diagnostic considerations.*

D1. In patients with muscular dystrophy who have proximal as well as distal weakness, clinicians should use specific clinical features (e.g., rippling muscles, cardiomyopathy, atrophy of specific muscle groups, irritability on EMG) and biopsy features (MFM, reduction of emerin immunostaining, presence of rimmed vacuoles) to guide genetic testing, which may include

mutations in the genes causing the various forms of MFM (see section on MFM), LGMD2B (dysferlin), LGMD2L (anoctamin-5), LGMD2J (titin), LGMD1C (caveolin-3), and EDMD (emerin and lamin A/C) (Level B).

Strength of Recommendation							
Modifier	R/U		C	B	A	Consensus	
Availability	Limited	0	Sometimes 2	Usually 3	Universal 3	No	
Financial burden	Prohibitive	0	Moderate 4	Minimal 4	None 0	Yes	
Variation in preferences	Large	0	Moderate 2	Small 3	Minimal 3	No	
Importance of outcomes	Not important	1	Somewhat Imp 2	Very Imp 4	Critical 1	No	
Benefit relative to Harm	Too Close	0	Modest 2	Moderate 5	Large 1	Yes	

  

Strength of Inference							
Element	Weak		Modest	Moderate	Strong	Consensus	
Internal inferences	<50%		≥50% to < 80%	≥80% to < 100%	100%	Yes	
Strong related evidence	<50%		≥50% to < 80%	≥80% to 100%	X	Yes	
Acceptance of Principles	<50%		≥50% to < 80%	≥80% to < 100%	100%	Yes	
Logical	<50%		≥50% to < 80%	≥ 80% to < 100%	100%	Yes	
Confidence in Evidence	Very Low		Low	Moderate	High	Yes	

There was substantial consensus after round 2. Based on the modifiers (availability, financial burden, variations), the panel selected Level B using informal consensus.

D2. In patients with suspected muscular dystrophy in whom initial genetic testing, muscle biopsy, and dried blood spot test for Pompe disease do not provide a diagnosis, clinicians may obtain genetic consultation or perform parallel sequencing of targeted exomes, whole-exome sequencing, whole-genome screening, or next-generation sequencing to identify the genetic abnormality (Level C).

Strength of Recommendation							
Modifier	R/U		C	B	A	Consensus	
Availability	Limited	1	Sometimes 6	Usually 1	Universal 0	Yes	
Financial burden	Prohibitive	3	Moderate 3	Minimal 2	None 0	No	
Variation in preferences	Large	3	Moderate 4	Small 1	Minimal 0	No	
Importance of outcomes	Not important	1	Somewhat Imp 4	Very Imp 3	Critical 0	No	
Benefit relative to Harm	Too Close	0	Modest 6	Moderate 2	Large 0	Yes	

  

Strength of Inference							
Element	Weak		Modest	Moderate	Strong	Consensus	
Internal inferences	<50%		≥50% to < 80%	≥80% to < 100%	100%	Yes	
Strong related evidence	<50%		≥50% to < 80%	≥80% to 100%	X	Yes	
Acceptance of Principles	<50%		≥50% to < 80%	≥80% to < 100%	100%	Yes	
Logical	<50%		≥50% to < 80%	≥ 80% to < 100%	100%	Yes	
Confidence in Evidence	Very Low		Low	Moderate	High	Yes	

There was substantial consensus after round 2. Based on the modifiers (availability, financial burden, variations), the panel selected Level C using informal consensus.

## Evaluation and Medical Management of Muscular Dystrophies

### Cardiac involvement in muscular dystrophies.

E1. Clinicians should refer newly diagnosed patients with

- a. LGMD1A, LGMD1B, LGMD1D, LGMD1E, LGMD2C–K, LGMD2M–P, BMD, EDMD, and MFM
  - b. muscular dystrophy without a specific genetic diagnosis
- for cardiology evaluation, including ECG and structural evaluation (echocardiography or cardiac MRI), even if they are asymptomatic from a cardiac standpoint, to guide appropriate management (Level B).

Strength of Recommendation									
Modifier	R/U		C		B	A	Consensus		
Availability	Limited	0	Sometimes	0	Usually	3	Universal	5	Yes
Financial burden	Prohibitive	0	Moderate	0	Minimal	6	None	2	Yes
Variation in preferences	Large	0	Moderate	0	Small	2	Minimal	6	Yes
Importance of outcomes	Not important	0	Somewhat Imp	0	Very Imp	4	Critical	4	Yes
Benefit relative to Harm	Too Close	0	Modest	0	Moderate	1	Large	7	Yes

Strength of Inference						
Element	Weak		Modest	Moderate	Strong	Consensus
Internal inferences	<50%		≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%		≥50% to < 80%	≥80% to 100%	x	Yes
Acceptance of Principles	<50%		≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%		≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low		Low	Moderate	High	Yes

E1a. If ECG or structural cardiac evaluation (e.g., echocardiography) is abnormal, or if the patient has episodes of syncope, near-syncope, or palpitations, clinicians should order rhythm evaluation (e.g., Holter monitor or event monitor) to guide appropriate management (Level B).

Strength of Recommendation									
Modifier	R/U		C		B		A	Consensus	
Availability	Limited	0	Sometimes	0	Usually	5	Universal	3	Yes
Financial burden	Prohibitive	0	Moderate	0	Minimal	6	None	2	Yes
Variation in preferences	Large	0	Moderate	0	Small	4	Minimal	4	Yes
Importance of outcomes	Not important	0	Somewhat Imp	0	Very Imp	3	Critical	5	Yes
Benefit relative to Harm	Too Close	0	Modest	0	Moderate	1	Large	7	Yes

Strength of Inference					
Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	x	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

E2. Clinicians should refer muscular dystrophy patients with palpitations or who are found to have symptomatic or asymptomatic tachycardia or arrhythmias for cardiology evaluation (Level B).

Strength of Recommendation										
Modifier		R/U		C		B		A		Consensus
Availability		Limited	0	Sometimes	1	Usually	4	Universal	3	No
Financial burden		Prohibitive	0	Moderate	0	Minimal	5	None	3	Yes
Variation in preferences		Large	0	Moderate	0	Small	2	Minimal	6	Yes
Importance of outcomes		Not important	0	Somewhat Imp	0	Very Imp	3	Critical	5	Yes
Benefit relative to Harm		Too Close	0	Modest	0	Moderate	2	Large	6	Yes

Strength of Inference					
Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	x	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

E3. Clinicians should refer muscular dystrophy patients with signs or symptoms of cardiac failure for cardiology evaluation (e.g., medical management, left ventricular assist device placement, or cardiac transplantation, as deemed necessary by the cardiologist) to prevent cardiac death (Level B).



Strength of Recommendation

Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	2	Usually	4	Universal	2	No
Financial burden	Prohibitive	0	Moderate	1	Minimal	5	None	2	No
Variation in preferences	Large	0	Moderate	0	Small	4	Minimal	4	Yes
Importance of outcomes	Not important	0	Somewhat Imp	0	Very Imp	3	Critical	5	Yes
Benefit relative to Harm	Too Close	0	Modest	0	Moderate	2	Large	6	Yes

Strength of Inference

Element	Weak		Modest		Moderate		Strong		Consensus
Internal inferences	<50%		≥50% to < 80%		≥80% to < 100%		100%		Yes
Strong related evidence	<50%		≥50% to < 80%		≥80% to 100%		X		Yes
Acceptance of Principles	<50%		≥50% to < 80%		≥80% to < 100%		100%		Yes
Logical	<50%		≥50% to < 80%		≥ 80% to < 100%		100%		Yes
Confidence in Evidence	Very Low		Low		Moderate		High		Yes

E4. It is not obligatory for clinicians to refer patients with LGMD2A, LGMD2B, and LGMD2L for cardiac evaluation unless they develop overt cardiac signs or symptoms (Level B).

Strength of Recommendation

Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	0	Usually	3	Universal	5	Yes
Financial burden	Prohibitive	0	Moderate	0	Minimal	2	None	6	Yes
Variation in preferences	Large	2	Moderate	1	Small	3	Minimal	2	No
Importance of outcomes	Not important	5	Somewhat Imp	1	Very Imp	2	Critical	0	No
Benefit relative to Harm	Too Close	1	Modest	3	Moderate	4	Large	0	Yes

Strength of Inference

Element	Weak		Modest		Moderate		Strong		Consensus
Internal inferences	<50%		≥50% to < 80%		≥80% to < 100%		100%		Yes
Strong related evidence	<50%		≥50% to < 80%		≥80% to 100%		X		Yes
Acceptance of Principles	<50%		≥50% to < 80%		≥80% to < 100%		100%		Yes
Logical	<50%		≥50% to < 80%		≥ 80% to < 100%		100%		Yes
Confidence in Evidence	Very Low		Low		Moderate		High		Yes

There was substantial consensus after round 2. Based on the modifiers (availability, financial burden, variations), the panel selected Level B using informal consensus.

E5. Clinicians should encourage female carriers of dystrophinopathy and emerinopathy to seek evaluation by a neuromuscular specialist and a cardiologist to assess for skeletal muscle and cardiac muscle involvement and to proactively treat cardiac involvement (Level B).

Strength of Recommendation											
Modifier		R/U		C		B		A		Consensus	
Availability		Limited	0	Sometimes	0	Usually	5	Universal	3	Yes	
Financial burden		Prohibitive	0	Moderate	0	Minimal	6	None	2	Yes	
Variation in preferences		Large	0	Moderate	1	Small	2	Minimal	5	No	
Importance of outcomes		Not important	0	Somewhat Imp	0	Very Imp	6	Critical	2	Yes	
Benefit relative to Harm		Too Close	0	Modest	0	Moderate	4	Large	4	Yes	

Strength of Inference											
Element		Weak		Modest		Moderate		Strong		Consensus	
Internal inferences		<50%		≥50% to < 80%		≥80% to < 100%		100%		Yes	
Strong related evidence		<50%		≥50% to < 80%		≥80% to 100%		x		Yes	
Acceptance of Principles		<50%		≥50% to < 80%		≥80% to < 100%		100%		Yes	
Logical		<50%		≥50% to < 80%		≥ 80% to < 100%		100%		Yes	
Confidence in Evidence		Very Low		Low		Moderate		High		Yes	

## Dysphagia and nutrition.

F1. Clinicians should refer muscular dystrophy patients with dysphagia, frequent aspiration, or weight loss for swallowing evaluation and/or gastroenterology evaluation to assess and manage swallowing function and aspiration risk, to teach patients techniques for safe and effective swallowing (e.g., “chin tuck” maneuver, altered food consistencies, etc.), and to consider placement of a gastrostomy/jejunostomy tube for nutritional support (Level B).

Strength of Recommendation										
Modifier		R/U	C	B	A	Consensus				
Availability		Limited	0	Sometimes	0	Usually	6	Universal	2	Yes
Financial burden		Prohibitive	0	Moderate	0	Minimal	7	None	1	Yes
Variation in preferences		Large	0	Moderate	0	Small	4	Minimal	4	Yes
Importance of outcomes		Not important	0	Somewhat Imp	0	Very Imp	7	Critical	1	Yes
Benefit relative to Harm		Too Close	0	Modest	0	Moderate	3	Large	5	Yes

Strength of Inference					
Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	x	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

## Pulmonary complications.

G1. Clinicians should order pulmonary function testing (spirometry and maximal inspiratory/expiratory force in the upright and, if normal, supine positions) or refer for pulmonary evaluation (to identify and treat respiratory insufficiency) in muscular dystrophy

patients at the time of diagnosis, or if they develop pulmonary symptoms later in their course (Level B).

Strength of Recommendation									
Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	0	Usually	5	Universal	3	Yes
Financial burden	Prohibitive	0	Moderate	0	Minimal	4	None	4	Yes
Variation in preferences	Large	0	Moderate	0	Small	3	Minimal	5	Yes
Importance of outcomes	Not important	0	Somewhat Imp	0	Very Imp	5	Critical	3	Yes
Benefit relative to Harm	Too Close	0	Modest	0	Moderate	1	Large	7	Yes

Strength of Inference					
Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

G1a. In patients with a known high risk of respiratory failure (e.g., those with LGMD2I or MFM), clinicians should obtain periodic pulmonary function testing (spirometry and maximal inspiratory/expiratory force in the upright position and, if normal, in the supine position) or evaluation by a pulmonologist to identify and treat respiratory insufficiency (Level B).

Strength of Recommendation									
Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	0	Usually	5	Universal	3	Yes
Financial burden	Prohibitive	0	Moderate	0	Minimal	4	None	4	Yes
Variation in preferences	Large	0	Moderate	0	Small	4	Minimal	4	Yes
Importance of outcomes	Not important	0	Somewhat Imp	0	Very Imp	6	Critical	2	Yes
Benefit relative to Harm	Too Close	0	Modest	0	Moderate	3	Large	5	Yes

Strength of Inference					
Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

G2. It is not obligatory for clinicians to refer patients with LGMD2B and LGMD2L for pulmonary evaluation or pulmonary function testing unless they are symptomatic (Level C).

Strength of Recommendation

Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	0	Usually	2	Universal	6	Yes
Financial burden	Prohibitive	0	Moderate	1	Minimal	1	None	6	No
Variation in preferences	Large	0	Moderate	3	Small	2	Minimal	3	No
Importance of outcomes	Not important	4	Somewhat Imp	3	Very Imp	1	Critical	0	No
Benefit relative to Harm	Too Close	1	Modest	3	Moderate	2	Large	2	Yes

Strength of Inference

Element	Weak		Modest		Moderate		Strong		Consensus
Internal inferences	<50%		≥50% to < 80%		≥80% to < 100%		100%		Yes
Strong related evidence	<50%		≥50% to < 80%		≥80% to 100%		X		Yes
Acceptance of Principles	<50%		≥50% to < 80%		≥80% to < 100%		100%		Yes
Logical	<50%		≥50% to < 80%		≥ 80% to < 100%		100%		Yes
Confidence in Evidence	Very Low		Low		Moderate		High		Yes

G3. Clinicians should refer muscular dystrophy patients with excessive daytime somnolence, nonrestorative sleep (e.g., frequent nocturnal arousals, morning headaches, excessive daytime fatigue), or respiratory insufficiency based on pulmonary function tests for pulmonary or sleep medicine consultation for consideration of noninvasive ventilation to improve quality of life (Level B).

Strength of Recommendation

Modifier	R/U		C		B		A		Consensus
Availability	Limited	0	Sometimes	1	Usually	5	Universal	2	No
Financial burden	Prohibitive	0	Moderate	0	Minimal	6	None	2	Yes
Variation in preferences	Large	0	Moderate	0	Small	5	Minimal	3	Yes
Importance of outcomes	Not important	0	Somewhat Imp	0	Very Imp	6	Critical	2	Yes
Benefit relative to Harm	Too Close	0	Modest	0	Moderate	3	Large	5	Yes

Strength of Inference

Element	Weak		Modest		Moderate		Strong		Consensus
Internal inferences	<50%		≥50% to < 80%		≥80% to < 100%		100%		Yes
Strong related evidence	<50%		≥50% to < 80%		≥80% to 100%		X		Yes
Acceptance of Principles	<50%		≥50% to < 80%		≥80% to < 100%		100%		Yes
Logical	<50%		≥50% to < 80%		≥ 80% to < 100%		100%		Yes
Confidence in Evidence	Very Low		Low		Moderate		High		Yes

### Cognitive dysfunction and learning disabilities.

H1. In muscular dystrophy patients with symptoms suggestive of cognitive dysfunction or learning disabilities, clinicians may order neuropsychological testing, MRI of the brain, and/or developmental pediatrics consultation to assess for and optimally manage CNS involvement (Level C).

Strength of Recommendation										
Modifier		R/U	C		B		A		Consensus	
Availability		Limited	0	Sometimes	2	Usually	5	Universal	1	No
Financial burden		Prohibitive	0	Moderate	3	Minimal	5	None	0	Yes
Variation in preferences		Large	0	Moderate	3	Small	3	Minimal	2	No
Importance of outcomes		Not important	1	Somewhat Imp	4	Very Imp	2	Critical	1	No
Benefit relative to Harm		Too Close	0	Modest	1	Moderate	6	Large	1	Yes

Strength of Inference					
Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	x	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

There was substantial consensus after round 2. Based on the modifiers (availability, financial burden, variations), the panel selected Level C using informal consensus.

## Spinal deformities.

I1. Clinicians should monitor patients with muscular dystrophy for the development of spinal deformities to prevent resultant complications and preserve function (Level B).

Strength of Recommendation									
Modifier	R/U		C		B		A	Consensus	
Availability	Limited	0	Sometimes	0	Usually	2	Universal	6	Yes
Financial burden	Prohibitive	0	Moderate	1	Minimal	5	None	2	No
Variation in preferences	Large	0	Moderate	0	Small	4	Minimal	4	Yes
Importance of outcomes	Not important	0	Somewhat Imp	1	Very Imp	6	Critical	1	Yes
Benefit relative to Harm	Too Close	0	Modest	0	Moderate	6	Large	2	Yes

Strength of Inference					
Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	x	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

I2. Clinicians should refer muscular dystrophy patients with musculoskeletal spine deformities to an orthopedic spine surgeon for monitoring and surgical intervention if it is deemed necessary in order to maintain normal posture, assist mobility, maintain cardiopulmonary function, and optimize quality of life (Level B).

Strength of Recommendation									
Modifier	R/U		C		B	A	Consensus		
Availability	Limited	0	Sometimes	1	Usually	6	Universal	1	Yes
Financial burden	Prohibitive	0	Moderate	2	Minimal	5	None	1	No
Variation in preferences	Large	0	Moderate	1	Small	6	Minimal	1	Yes
Importance of outcomes	Not important	0	Somewhat Imp	0	Very Imp	7	Critical	1	Yes
Benefit relative to Harm	Too Close	0	Modest	0	Moderate	7	Large	1	Yes

Strength of Inference						
Element	Weak		Modest	Moderate	Strong	Consensus
Internal inferences	<50%		≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%		≥50% to < 80%	≥80% to 100%	x	Yes
Acceptance of Principles	<50%		≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%		≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low		Low	Moderate	High	Yes

## Osteoporosis.

J1. Clinicians may choose to evaluate patients with restricted mobility due to muscular dystrophy with bone density studies for osteoporosis in order to institute timely management and minimize fractures (Level C).

Strength of Recommendation										
Modifier		R/U	C	B		A		Consensus		
Availability		Limited	0	Sometimes	1	Usually	5	Universal	2	No
Financial burden		Prohibitive	0	Moderate	1	Minimal	7	None	0	Yes
Variation in preferences		Large	0	Moderate	1	Small	3	Minimal	4	No
Importance of outcomes		Not important	0	Somewhat Imp	2	Very Imp	5	Critical	1	No
Benefit relative to Harm		Too Close	0	Modest	2	Moderate	3	Large	3	Yes

Strength of Inference					
Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	x	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

There was substantial consensus after round 2. Based on the modifiers (availability, financial burden, variations), the panel selected Level C using informal consensus.

## Infection prophylaxis.

K1. Clinicians should recommend pneumococcal polysaccharide vaccine (PPSV23) as per the CDC schedule<sup>e514</sup> and annual influenza vaccine to patients with muscular dystrophy in order to prevent respiratory complications of pneumococcal pneumonia and influenza (Level B).

Strength of Recommendation											
Modifier		R/U		C		B		A		Consensus	
Availability		Limited	0	Sometimes	0	Usually	2	Universal	6	Yes	
Financial burden		Prohibitive	0	Moderate	0	Minimal	4	None	4	Yes	
Variation in preferences		Large	0	Moderate	1	Small	3	Minimal	4	No	
Importance of outcomes		Not important	0	Somewhat Imp	1	Very Imp	6	Critical	1	Yes	
Benefit relative to Harm		Too Close	0	Modest	1	Moderate	3	Large	4	Yes	

Strength of Inference											
Element		Weak		Modest		Moderate		Strong		Consensus	
Internal inferences		<50%		≥50% to < 80%		≥80% to < 100%		100%		Yes	
Strong related evidence		<50%		≥50% to < 80%		≥80% to 100%		x		Yes	
Acceptance of Principles		<50%		≥50% to < 80%		≥80% to < 100%		100%		Yes	
Logical		<50%		≥50% to < 80%		≥ 80% to < 100%		100%		Yes	
Confidence in Evidence		Very Low		Low		Moderate		High		Yes	

## Rehabilitative Management and Treatment of Muscular Dystrophies

### Clinical rehabilitative management.

L1. Clinicians should refer patients with muscular dystrophy to a clinic that has access to multiple specialties (e.g., physical therapy, occupational therapy, respiratory therapy, speech and swallowing therapy, cardiology, pulmonology, orthopedics, and genetics) designed specifically to care for patients with muscular dystrophy and other neuromuscular disorders in order to provide efficient and effective long-term care (Level B).

Strength of Recommendation										
Modifier		R/U	C		B		A		Consensus	
Availability		Limited	0	Sometimes	2	Usually	6	Universal	0	Yes
Financial burden		Prohibitive	0	Moderate	2	Minimal	5	None	1	No
Variation in preferences		Large	0	Moderate	2	Small	6	Minimal	0	Yes
Importance of outcomes		Not important	0	Somewhat Imp	2	Very Imp	6	Critical	0	Yes
Benefit relative to Harm		Too Close	0	Modest	0	Moderate	5	Large	3	Yes

Strength of Inference					
Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	x	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

L2. Clinicians might discuss opportunities for participation in clinical trials, if available, with muscular dystrophy patients (Level C).

Strength of Recommendation										
Modifier		R/U	C		B		A		Consensus	
Availability		Limited	0	Sometimes	4	Usually	1	Universal	3	No
Financial burden		Prohibitive	0	Moderate	1	Minimal	4	None	3	
Variation in preferences		Large	1	Moderate	2	Small	4	Minimal	1	
Importance of outcomes		Not important	1	Somewhat Imp	0	Very Imp	7	Critical	0	Yes
Benefit relative to Harm		Too Close	0	Modest	1	Moderate	5	Large	2	Yes

Strength of Inference						
Element	Weak	Modest		Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%		≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%		≥80% to 100%	x	Yes
Acceptance of Principles	<50%	≥50% to < 80%		≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%		≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low		Moderate	High	Yes

There is a persistent, substantial lack of consensus regarding availability. The recommendation defaults to Level C.

L3. Clinicians should recommend that patients with muscular dystrophy have periodic assessments by a physical and occupational therapist for symptomatic and preventive screening (Level B).

Strength of Recommendation									
Modifier	R/U		C		B		A	Consensus	
Availability	Limited	0	Sometimes	0	Usually	6	Universal	2	Yes
Financial burden	Prohibitive	0	Moderate	1	Minimal	7	None	0	Yes
Variation in preferences	Large	0	Moderate	1	Small	5	Minimal	2	No
Importance of outcomes	Not important	0	Somewhat Imp	3	Very Imp	5	Critical	0	Yes
Benefit relative to Harm	Too Close	0	Modest	0	Moderate	6	Large	2	Yes

Strength of Inference									
Element	Weak		Modest		Moderate		Strong		Consensus
Internal inferences	<50%		≥50% to < 80%		≥80% to < 100%		100%		Yes
Strong related evidence	<50%		≥50% to < 80%		≥80% to 100%		x		Yes
Acceptance of Principles	<50%		≥50% to < 80%		≥80% to < 100%		100%		Yes
Logical	<50%		≥50% to < 80%		≥ 80% to < 100%		100%		Yes
Confidence in Evidence	Very Low		Low		Moderate		High		Yes

L4. While respecting and protecting patient autonomy, clinicians should proactively anticipate and facilitate patient and family decision making as the disease progresses, including decisions regarding loss of mobility, need for assistance with activities of daily living, medical complications, and end-of-life care (Level B).



Strength of Recommendation							
Modifier	R/U		C		B	A	Consensus
Availability	Limited	0	Sometimes	0	Usually	0	Universal 8
Financial burden	Prohibitive	0	Moderate	0	Minimal	2	None 6
Variation in preferences	Large	0	Moderate	0	Small	4	Minimal 4
Importance of outcomes	Not important	0	Somewhat Imp	0	Very Imp	4	Critical 4
Benefit relative to Harm	Too Close	0	Modest	0	Moderate	1	Large 7

  

Strength of Inference					
Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

L5. For patients with muscular dystrophy, clinicians should prescribe physical and occupational therapy, as well as bracing and assistive devices that are adapted specifically to the patient's deficiencies and contractures, in order to preserve mobility and function and prevent contractures (Level B).

Strength of Recommendation							
Modifier	R/U		C		B	A	Consensus
Availability	Limited	0	Sometimes	0	Usually	7	Universal 1
Financial burden	Prohibitive	0	Moderate	1	Minimal	7	None 0
Variation in preferences	Large	0	Moderate	1	Small	3	Minimal 4
Importance of outcomes	Not important	0	Somewhat Imp	0	Very Imp	8	Critical 0
Benefit relative to Harm	Too Close	0	Modest	0	Moderate	4	Large 4

  

Strength of Inference					
Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	X	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

### Strength training and aerobic exercise training.

M1. Clinicians may advise patients with muscular dystrophy that aerobic exercise combined with a supervised submaximal strength training program is probably safe (Level C).

Strength of Recommendation										
Modifier		R/U	C		B		A		Consensus	
Availability		Limited	0	Sometimes	1	Usually	3	Universal	4	No
Financial burden		Prohibitive	0	Moderate	2	Minimal	4	None	2	No
Variation in preferences		Large	1	Moderate	3	Small	3	Minimal	1	No
Importance of outcomes		Not important	0	Somewhat Imp	4	Very Imp	4	Critical	0	Yes
Benefit relative to Harm		Too Close	0	Modest	1	Moderate	6	Large	1	Yes

Strength of Inference						
Element	Weak	Modest		Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%		≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%		≥80% to 100%	x	Yes
Acceptance of Principles	<50%	≥50% to < 80%		≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%		≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low		Moderate	High	Yes

There was substantial consensus after round 2. Based on the modifiers (availability, financial burden, variations), the panel selected Level C using informal consensus.

M2. Clinicians may advise patients with muscular dystrophy that gentle, low-impact aerobic exercise (swimming, stationary bicycling) improves cardiovascular performance, increases muscle efficiency, and lessens fatigue (Level C).

Strength of Recommendation										
Modifier		R/U	C		B		A		Consensus	
Availability		Limited	0	Sometimes	1	Usually	4	Universal	3	No
Financial burden		Prohibitive	0	Moderate	0	Minimal	4	None	4	Yes
Variation in preferences		Large	1	Moderate	4	Small	3	Minimal	0	No
Importance of outcomes		Not important	0	Somewhat Imp	4	Very Imp	4	Critical	0	Yes
Benefit relative to Harm		Too Close	0	Modest	2	Moderate	4	Large	2	Yes

Strength of Inference						
Element	Weak	Modest		Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%		≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%		≥80% to 100%	x	Yes
Acceptance of Principles	<50%	≥50% to < 80%		≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%		≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low		Moderate	High	Yes

There was substantial consensus after round 2. Based on the modifiers (availability, financial burden, variations), the panel selected Level C using informal consensus.

M3. Clinicians may counsel patients with muscular dystrophy to hydrate adequately, not to exercise to exhaustion, and to avoid supramaximal, high-intensity exercise (Level C).

Strength of Recommendation										
Modifier		R/U	C		B		A		Consensus	
Availability		Limited	0	Sometimes	0	Usually	1	Universal	7	Yes
Financial burden		Prohibitive	0	Moderate	0	Minimal	1	None	7	Yes
Variation in preferences		Large	0	Moderate	0	Small	5	Minimal	3	Yes
Importance of outcomes		Not important	0	Somewhat Imp	4	Very Imp	3	Critical	1	No
Benefit relative to Harm		Too Close	0	Modest	0	Moderate	5	Large	3	Yes

Strength of Inference						
Element	Weak	Modest		Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%		≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%		≥80% to 100%	x	Yes
Acceptance of Principles	<50%	≥50% to < 80%		≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%		≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low		Moderate	High	Yes

There was substantial consensus after round 2. Based on the modifiers (availability, financial burden, variations), the panel selected Level C using informal consensus.

M4. Clinicians should educate patients with muscular dystrophy who are participating in an exercise program about the warning signs of overwork weakness and myoglobinuria, which include feeling weaker rather than stronger within 30 minutes after exercise, excessive muscle soreness 24–48 hours following exercise, severe muscle cramping, heaviness in the extremities, and prolonged shortness of breath (Level B).

Strength of Recommendation										
Modifier		R/U		C		B		A		Consensus
Availability		Limited	0	Sometimes	0	Usually	2	Universal	6	Yes
Financial burden		Prohibitive	0	Moderate	0	Minimal	1	None	7	Yes
Variation in preferences		Large	0	Moderate	0	Small	4	Minimal	4	Yes
Importance of outcomes		Not important	0	Somewhat Imp	2	Very Imp	4	Critical	2	No
Benefit relative to Harm		Too Close	0	Modest	0	Moderate	3	Large	5	Yes

Strength of Inference					
Element	Weak	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Strong related evidence	<50%	≥50% to < 80%	≥80% to 100%	x	Yes
Acceptance of Principles	<50%	≥50% to < 80%	≥80% to < 100%	100%	Yes
Logical	<50%	≥50% to < 80%	≥ 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

## Medical treatments.

N1. Clinicians should not offer patients with LGMD gene therapy outside of a research study designed to determine the efficacy and safety of the treatment (Level R).

N2. Clinicians should not offer patients with LGMD neutralizing antibody to myostatin outside of a research study designed to determine the efficacy and safety of the treatment (Level R).

N3. Clinicians should not offer patients with BMD myoblast transplantation or subcutaneous growth hormone injections outside of a research study designed to determine the efficacy and safety of the treatment (Level R).

Level R determinations based on insufficient evidence regarding efficacy and judgment of high cost or risk of interventions.