Evidence-based Guideline: Evaluation, Diagnosis, and Management of

Facioscapulohumeral Muscular Dystrophy

Report of the Guideline Development, Dissemination, and Implementation 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

ABBREVIATIONS

AAN: American Academy of Neurology

AANEM: American Association of the Neuromuscular & Electrodiagnostic Medicine

CI: confidence interval

DUX4: double homeobox 4

EVID: statements supported directly by the systematically reviewed evidence

FSHD: facioscapulohumeral muscular dystrophy

FSHD1: FSHD type 1

FSHD2: FSHD type 2

FVC: forced vital capacity

GDDI: Guideline Development, Dissemination, and Implementation Subcommittee

INFER: an inference from one or more of the other statements

kb: kilobase

MD: muscular dystrophy

MYO-029: myostatin inhibitor

PFT: pulmonary function testing

PIRP: Practice Issues Review Panel

poly-A: polyadenylation

PRIN: an accepted axiom or principle

QMT: quantitative isometric myometry test

QOL: quality of life

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

SD: standard deviation

ABSTRACT

Objective: To develop recommendations for the evaluation, diagnosis, prognostication, and treatment of facioscapulohumeral muscular dystrophy (FSHD) from a systematic review and analysis of the evidence.

Methods: Relevant articles were analyzed in accordance with the American Academy of Neurology classification of evidence schemes for diagnostic, prognostic, and treatment studies. Recommendations were linked to the strength of the evidence and other factors.

Results and recommendations: Available genetic testing for FSHD type 1 is highly sensitive and specific. Although respiratory insufficiency occurs rarely in FSHD, patients with severe FSHD should have routine pulmonary function testing. Routine cardiac screening is not necessary in patients with FSHD without cardiac symptoms. Symptomatic retinal vascular disease is very rare in FSHD. Exudative retinopathy, however, is potentially preventable, and patients with large deletions should be screened through dilated indirect ophthalmoscopy. The prevalence of clinically relevant hearing loss is not clear. In clinical practice, patients with childhood-onset FSHD may have significant hearing loss. Because undetected hearing loss may impair language development, screening through audiometry is recommended for such patients. Musculoskeletal pain is common in FSHD, and treating physicians should routinely inquire about pain. There is at present no effective pharmacologic intervention in FSHD. Available studies suggest that scapular fixation is safe and effective. However, these studies used different surgical approaches and rarely defined patient selection criteria. Surgical scapular fixation might be cautiously offered to selected patients. Aerobic exercise in FSHD appears to be safe and potentially beneficial. On the basis of the evidence, patients with FSHD might be encouraged to engage in low-intensity aerobic exercises.

INTRODUCTION

Facioscapulohumeral muscular dystrophy (FSHD) is the third most common form of muscular dystrophy (MD), with a prevalence of approximately 1:15,000–1:20,000.[e1,e2] It is an autosomal dominant disorder; however, up to 30% of cases are sporadic, arising from de novo mutations. FSHD is characterized by a distinctive, initially regional distribution of muscle involvement. As the name implies, facial, periscapular, and humeral muscles typically are involved early in the disease course, although the deltoids are spared. This regional involvement, often asymmetric, leads to a distinctive appearance to the shoulders of straight clavicles and scapular winging on attempted shoulder abduction or forward flexion.[e3]

FSHD symptoms typically develop in the second decade of life but can begin at any age from infancy to late adulthood. As many as one-third of patients are asymptomatic, with the diagnosis made on the basis of previously unrecognized physical examination signs, present in more than 90% of patients by the age of 20.[e1]

Shoulder girdle weakness, often asymmetric, is the most common presenting symptom. Weakness progresses in a descending manner to involve the upper arm muscles, then the trunk and abdomen, and then the lower extremities, especially the ankle dorsiflexors.

FSHD typically progresses slowly but variably.[e4,e5] About 20% of individuals with FSHD become wheelchair dependent after age 50.[e1] Clinically relevant extramuscular manifestations are uncommon in FSHD but can include respiratory compromise; retinal vascular disease that, in rare cases, leads to an exudative retinopathy and visual loss; hearing loss; and, possibly, an increased incidence of cardiac arrhythmias.

The molecular genetic basis of FSHD is complex. At the tip of chromosome 4q35 lies a repetitive 3.3 kb DNA sequence known as D4Z4 repeats.[e6,e7] Moreover, there are 2 different

DNA variants distal to the D4Z4 repeats, called the A and B allelic variants.[e8] FSHD type 1 (FSHD1), accounting for 95% of FSHD cases, results from deletion of a critical number of D4Z4 repeats, but only when this occurs on the A allele. The biological basis for this dual requirement is becoming increasingly understood. Contraction of the D4Z4 repeat results in a more open chromatin structure, allowing the potential expression of gene sequences within the repeats. One such gene, double homeobox 4 (DUX4), lacks the polyadenylation (poly-A) sequence required to produce stable messenger RNA.[e9,e10] Because only the A (not the B) allele variant contains a poly-A sequence, stable DUX4 expression can occur only in the presence of the A allelic variant.[e11,e12]

Complicating matters is the existence of a genetically distinct but clinically identical FSHD type—FSHD type 2 (FSHD2)—now known to account for approximately 5% of patients with clinically defined FSHD.[e13,e14] Unlike the majority of patients with FSHD (i.e., FSHD1), patients with FSHD2 do not have contractions in the 4q35 D4Z4. As with FSHD1, and despite a normal number of repeats, the chromatin structure at the D4Z4 repeats is more open, and at least one 4q35 allele is an A variant.[e13] Recent studies have implicated mutations in SMCHD1, a gene on chromosome 18 that functions as a chromatin modifier, as the cause of the D4Z4 chromatin changes observed in about 85% of patients with FSHD2.[e15] Comprehensive molecular genetic testing for FSHD2 is complex and not readily available currently, and thus is not addressed in this guideline.

Despite having distinct genotypes, FSHD1 and FSHD2 have an identical molecular basis that results from the aberrant expression of the DUX4 gene in skeletal muscle.[e15,e16] DUX4 protein is a transcription factor normally expressed only in the germline, but little is known about its function.[e17] Preliminary evidence suggests that inappropriate expression of DUX4 and its

transcriptional targets in skeletal muscle can result in apoptosis, impaired muscle regeneration, and induction of an immune response.[e17]

The clinical diagnosis of FSHD is based on the presence of a characteristic distribution of muscle weakness and is easily confirmed in most instances of FSHD1 by genetic testing. To date there is no effective treatment for muscle weakness in FSHD. Standard disease management includes physical therapy, bracing for foot drop, surgical scapular fixation in some patients, management of respiratory complications, and management and symptomatic treatment of extramuscular manifestations.

Previous FSHD practice guidelines have been based on consensus and expert opinion.[e18,e19] The present guideline, based on systematic review of the evidence, focuses exclusively on FSHD. Duchenne MD and myotonic dystrophy will be discussed in forthcoming guidelines; limb-girdle muscular dystrophy and congenital MD are addressed in separate guidelines.[e20,e21] The present guideline addresses the following practical issues related to FSHD (reflective only of evidence relevant to FSHD1; no large FSHD2 clinical studies exist):

1. In regard to genetic testing, for patients with clinically defined FSHD (as determined by explicitly stated clinical criteria substantially similar to the consortium criteria),[e22] how often does D4Z4 contraction on 4q35 confirm the diagnosis of FSHD (irrespective of its occurrence on an allele A background)? For individuals who do not have FSHD, how often is a D4Z4 contraction on 4q35 found? For individuals who do not have FSHD, how often is a D4Z4 contraction on 4q35 on allele A found?

2. Among patients with FSHD, which factors are associated with or predict loss of clinically meaningful milestones (e.g., loss of independent ambulation)?

3. Among patients with FSHD, how frequent are respiratory abnormalities, cardiac abnormalities, retinal disease, hearing loss, and pain?

4. In regard to treatment, do interventions (as compared with no intervention) improve patient-relevant outcomes? Are there features that identify patients who are more or less likely to improve with a specific intervention?

DESCRIPTION OF THE ANALYTIC PROCESS

In July 2010, the Guideline Development, Dissemination, and Implementation Subcommittee (GDDI) of the American Academy of Neurology (AAN) and the Practice Issues Review Panel (PIRP) of the American Association of the Neuromuscular & Electrodiagnostic Medicine (AANEM) convened a panel of clinicians with expertise in FSHD (see appendices e-1 and e-2 for a listing of the members of the AAN GDDI and AANEM PIRP). In accordance with the processes outlined in the 2004 and 2011 AAN guideline development manuals,[e23,e24] the panel searched the Medline, EMBASE, Cochrane, and Scopus databases from 1948 to October 2012 for relevant peer-reviewed articles in humans and in all languages (see appendix e-3 for search strategies). The initial search yielded 977 abstracts. Of those, 176 were obtained for full-text review. Each of the 176 articles was reviewed by 2 panel members working independently of each other. A total of 94 articles were selected for inclusion in the analysis, and of those, 76 articles were selected for evidence rating. An updated literature search completed in January 2014 identified an additional 12 potentially relevant articles, 4 of which were selected for evidence rating.

Selected articles contained information relevant to the 4 questions posed above and had acceptable study designs, including randomized, controlled trials; cohort studies; case-control

studies; and case series. Reviews and meta-analyses were excluded, as were studies with 6 or fewer participants for studies of FSHD complications and prognosis, fewer than 9 participants for genetic screening, and fewer than 5 participants for treatment. Also excluded were studies not relevant to the clinical questions, studies including participants who had unrelated diseases or were outside of the study population, and articles that were not peer reviewed. Each of the 76 articles was rated by 2 panel members using the AAN criteria for classification of screening, prognostic, and treatment articles (appendix e-4).

The panel formulated a rationale for recommendations based on the evidence systematically reviewed and stipulated axiomatic principles of care. This rationale is explained in a section that precedes each set of recommendations. From this rationale, corresponding actionable recommendations were inferred. The level of obligation of the recommendations was assigned using a modified Delphi process that considered the following prespecified domains: the confidence in the evidence systematically reviewed, the acceptability of axiomatic principles of care, the strength of indirect evidence, and the relative magnitude of benefit to harm. Additional factors explicitly considered by the panel that could modify the level of obligation include judgments regarding the importance of outcomes, cost of compliance with the recommendation relative to benefit, the availability of the intervention, and anticipated variations in patients' preferences. The prespecified rules for determining the final level of obligation from these domains are indicated in appendix e-5. The level of obligation was indicated using standard modal operators. *Must* corresponds to *Level A*, very strong recommendations; *should* to *Level B*, strong recommendations; and *might* to *Level C*, weak recommendations. The panel members' judgments supporting the levels of obligation are indicated in appendix e-6.

ANALYSIS OF EVIDENCE

FSHD genetic testing.

Clinical questions.

Understanding the molecular genetics of FSHD1 is critical to the molecular diagnosis of this disorder. Healthy individuals possess at least 11 D4Z4 repeats, yielding a DNA fragment >38 kb on standard genetic testing. Affected individuals, in contrast, possess between 1 and 10 repeats, yielding DNA fragments 10 to 38 kb in size.[e7] Measurement of the size of the residual D4Z4 sequence on 4q35 forms the basis for genetic testing in FSHD. As previously discussed, an additional requirement for FSHD identification is that the contraction occur on the A allelic variant. Routine first-pass commercial genetic testing in the United States measures the residual D4Z4 repeat sizes without determining the A or B allelic variants. The prevalence of D4Z4 repeat sizes in the range of 1 to 10 alleles is low in the general population. This low prevalence raises questions about the clinical utility of routine determination of the A/B variant in molecular confirmation of FSHD. The following specific clinical questions were examined:

- For patients with clinically defined FSHD (as determined by explicitly stated clinical criteria substantially similar to the consortium criteria), how often does D4Z4 contraction on 4q35 confirm the diagnosis of FSHD (irrespective of its occurrence on an allele A background)?

- For individuals who do not have FSHD, how often is a D4Z4 contraction on 4q35 found?

- For individuals who do not have FSHD, how often is a D4Z4 contraction on 4q35 on allele A found?

Analysis.

Nine Class III studies containing information relevant to the questions above were reviewed.[e25–e33] The studies were rated Class III primarily because the patient populations studied were recruited from specialty clinics, which increases the risk of referral bias.

All 9 Class III studies addressed the question of the sensitivity of the D4Z4 contraction on 4q35 for the diagnosis of FSHD.[e25–e33] In these studies FSHD was defined by standard clinical criteria. In most of the studies the deletion was detected by measurement of allele size through use of the standard p13E-11 probe proximal to the D4Z4 repeat and genomic DNA digested with EcoRI and BlnI restriction enzymes. The frequency of D4Z4 contractions among patients with clinically defined FSHD ranged from 86% to 100%. There was statistical heterogeneity in the results (I^2 = 0.65). Some of the heterogeneity in the studies could be accounted for by the varying definitions for the upper limit in the size of a deleted allele (range: 28–38 kb). The pooled estimate of the sensitivity of the presence of D4Z4 contraction (random effects) was 93% (95% confidence interval [CI] 88%–96%). The confidence in the evidence was graded as moderate (upgraded from low because of the magnitude of the effect).

These 9 studies also contained evidence in regard to the specificity of the presence of the D4Z4 contraction.[e25–e33] One of the studies was excluded because the genetic testing was done using a single digestion with EcoRI, which could result in false-positive contraction on the homologous region on chromosome 10.[e28] The frequency of D4Z4 contractions in normal controls ranged from 0% to 9%. The pooled estimate of the specificity of the presence of D4Z4 contraction (random effects) was 99% (95% CI 97%–100%). The confidence in the evidence was graded as moderate (upgraded from low because of the magnitude of the effect).

A single Class III study contained evidence in regard to the specificity of the presence of a D4Z4 contraction on an A allele background.[e29] This study found that 11 out of 801 normal individuals

carried a contracted allele on an A allele background (specificity 98%; 95% CI 97.5%–99.2%). The confidence in the evidence was graded as low (upgraded from very low because of the magnitude of the effect).

Conclusions.

The finding of a D4Z4 contraction on chromosome 4q35 likely has a sensitivity of 93% and a specificity of 98% for the diagnosis of clinically defined FSHD (9 Class III studies).[e25–e33] In a patient population with clinically defined FSHD, the degree of specificity is not likely to be further enhanced by testing for presence of the A variant.

Risk factors for disease severity.

Clinical question.

A critical aspect of management of patients with any neuromuscular disorder lies in identifying clinical, biochemical, or genetic aspects of the illness associated with prognosis. It is indispensable to identify such risk factors that might be linked to a severe (or more benign) course when discussing prognosis with patients, designing therapy programs and other meaningful interventions, and helping patients make important medical, financial, and other life decisions. This is true particularly in a disease such as FSHD where there is tremendous variability in the extent and severity of involvement. For this analysis, relevant studies were reviewed to address the following specific question: Among patients with FSHD, which factors are associated with or predict loss of clinically meaningful milestones (e.g., loss of independent ambulation)?

Analysis.

Seven studies containing information relevant to this question were reviewed.[e30,e34–e39] One study was performed before accurate genetic testing was available and was not considered further.[e36] The remaining studies explored the prognostic effects of 2 risk factors: age at symptom onset and D4Z4 repeat size. Five studies examined the relationship between D4Z4 repeat size and severity.[e30,e34,e35,e38,e39] A Class I study in a cohort of 313 patients showed a linear relationship between age at diagnosis and repeat size. The study also showed that the age at which patients started using wheelchairs is associated with D4Z4 repeat size: 24.1 years (CI 17.0–31.3) for repeat sizes of <18 kb, 48 years (CI 44.0–52.3) for repeat sizes of 19 to 28 kb, and 58.6 years (CI 52.2–64.9) for repeat sizes of > 28 kb.[e38] A Class II study found a similar correlation between age at loss of ambulation and repeat size ($r = 0.773$, $p < 0.001$).[e39] Another Class II study in a cohort of 165 patients with FSHD found an inverse correlation between fragment size and clinical severity as assessed by degree of leg weakness and a global clinical severity score.[e30] Severe lower-limb involvement was found in 100% of patients with an EcoRI fragment size of 10 to 13 kb, in 53% of patients with a fragment size of 16 to 20 kb, and in only 19% of patients with a fragment size larger than 21 kb. In this study 36% of the variation in the severity of lower-limb involvement was explained by fragment size. There was no significant correlation found between fragment size and age at loss of ambulation. In a Class III study of 7 de novo patients, quantitative isometric myometry test (QMT) scores normalized for age, sex, and height were used to quantify overall disease severity. This analysis found a significant ($r = 0.92$, $p < 0.004$) correlation between disease severity and the size of the 4q35-associated deletion.[e36] A Class II study of 65 patients, however, found no correlation between Clinical Severity Scale scores and fragment size or between fragment size and physical function on the SF-36 quality of life (QOL)

scale; however, on the physical function subscore of this scale, patients with fragment sizes <18 kb had lower scores (*p* value not reported).[e37]

A single Class III study addressed the question of whether age at onset affected disease severity.[e34] This study found a significant correlation between proband age at onset and FSHD-associated fragment size ($r = 0.56$, $p < 0.001$). A similar correlation ($r = 0.70$, $p < 0.01$) with fragment size was observed for age at loss of ambulation in 16 patients using a wheelchair.

Conclusions.

In patients with FSHD, smaller D4Z4 repeat size is probably associated with more severe disease as measured by age at diagnosis and age at wheelchair dependence (1 Class I study).[e38] Other measures of disease severity possibly associated with smaller fragment size include quantitative computerized muscle testing, severity of leg weakness, global severity scores, and earlier loss of ambulation (one Class II study or multiple Class III studies).[e30,e34,e35,e39] Earlier age at onset is also possibly associated with smaller fragment size and earlier loss of ambulation (one Class III study).[e34] Patients with very large deletions (EcoRI fragment sizes of 10–15 kb) are particularly prone to severe disease.

Complications.

Clinical question.

Although the cardinal features of FSHD involve limb weakness that starts with focal weakness of the shoulders, face, and humeral muscles, additional systemic features may occur. These extramuscular features may have significant and, at times, life-threatening consequences. It is important for clinicians to recognize the association between these manifestations and the presence of FSHD so that needed monitoring, counseling, and early interventions may be

implemented. The following specific clinical question was examined: Among patients with FSHD, how frequent are respiratory abnormalities, cardiac abnormalities, retinal disease, hearing loss, and pain?

Analysis.

Respiratory abnormalities. One Class II study, 1 Class III study, and 1 Class IV study were analyzed.[e36,e40,e41] In the Class II study, 10 patients with FSHD with respiratory insufficiency requiring nocturnal ventilator support were identified in a Dutch FSHD population of 800 patients, representing an estimated prevalence of 1.25% (95% CI 0.5%–2%).[e40] The Class III study examined pulmonary function testing (PFT) in 23 of 53 patients with FSHD.[e36] All patients had clinically defined FSHD, but it was not genetically confirmed. Of the 23 patients tested, 3 or 13% (95% CI 0.7%–27%) had a severe restrictive pattern on PFT. In contrast, the Class IV study selected 16 patients with genetically confirmed FSHD who were ambulant but severely affected and found only mild signs of a restrictive pattern on PFT in some patients (forced vital capacity [FVC] range 85%–117% predicted).[e41]

Cardiac abnormalities. Four Class III studies using electrocardiography/echocardiography found no structural abnormalities in 80 patients with FSHD (95% CI 0%–4.6%).[e42–e45] Six Class III studies examined surface electrocardiogram/echocardiogram in a combined total of 227 patients with FSHD.[e36,e42–e46] Abnormalities were found in 89 or 39.2% (95% CI 33.1%–45.7%) of patients screened. The same 6 Class III studies looked at the frequency of symptomatic or inducible supraventricular arrhythmias and found these in 22 patients or 9.7% (95% CI 6.5%–14.2%).

Retinal vascular disease. Four Class III studies examined the frequency of retinal vascular abnormalities on dilated eye examination or fluorescein angiography in 294 patients.[e47–e50] Of

those screened, 15 or 25% (95% CI 20.9%–30.8%) had retinal vascular abnormalities. One of the Class III studies, examining 396 patients with genetically confirmed FSHD, identified 3 patients with symptomatic retinal vascular disease.[e50] For the 4 studies, the combined proportion of patients with FSHD who had symptomatic retinal disease is 0.6% (95% CI 0.2%–1.5%).[e47–e50] In the previously mentioned study, a patient survey and literature review of patients with FSHD who had Coats disease, a total of 14 patients were identified; all but one had very large deletions (< 20 kb).[e50]

Hearing loss. Eight Class III studies used audiometry to examine hearing in a combined total of 394 patients. Of the patients examined, 61 or 15.5% (95% CI 12.1%–19.4%) had audiometric abnormalities.[e26,e33,e47–e49,e51–e53] In one of the studies, 3 of 4 patients followed with sequential audiometry over a 5-year period showed worsening hearing loss by audiogram.[e53] In addition, as in symptomatic retinal vascular disease, hearing loss occurs only in patients with large deletions (≤20 kb); hearing loss occurs in 32% (95% CI 16.7%–51.4%) of patients with large deletions.[e53] This observation is supported by a study of patients with FSHD and both symptomatic retinal vasculopathy and large deletion size.[e50] Of the 14 patients identified, 57% (95% CI 29.0%–82.3%) had hearing loss, 35.7% of whom required hearing aids.[e50]

Pain. One Class II study and 2 Class III studies examined the frequency of pain in a combined total of 376 patients with FSHD.[e37,e54,e55] Of those surveyed, 297 or 79% (95% CI 74.6%–82.8%) complained of pain. A single study assessed the severity of pain. Of 65 patients in that study, 8 or 10.8% (95% CI 3.2%–18.3%) had clinically significant pain.[e37] The most common sites of pain are, in descending order, the lower back, the legs, the shoulders, and the neck.[e54]

Conclusions.

Respiratory abnormalities. Evidence suggests that respiratory insufficiency and reduced pulmonary function may occur. However, there is insufficient evidence to determine the frequency and severity of respiratory compromise in patients with FSHD (1 Class II study[e40] and 1 Class III study[e36]).

Cardiac abnormalities. The prevalence of structural cardiac abnormalities on electrocardiography/echocardiography is possibly zero, but precision of this estimate cannot exclude a frequency of up to 4.6%. Although symptomatic or inducible supraventricular arrhythmias are found in patients with FSHD, because of the risk of referral bias there is insufficient evidence to determine the frequency of clinically relevant supraventricular arrhythmias (multiple Class III studies).[e36,e42–e46]

Retinal vascular disease. Confidence in the evidence for the prevalence of retinal vascular abnormalities is low, with up to 25% (95% CI 20.9%–30.8%) showing abnormalities on examination. However, only 0.6% (95% CI 0.2%–1.5%) of patients with FSHD develop symptomatic retinal disease (4 Class III studies).[e47–e50]

Hearing loss. Confidence in the evidence for the prevalence of audiometric abnormalities is very low due to the wide range of prevalence reported, ranging from rates equivalent to a normal matched control population to a prevalence of 64%. One study that correlated hearing loss with genotype suggests that only patients with large deletions, who represent about 15% of all patients with FSHD, are susceptible to hearing loss.[e53] Poor representation of this subgroup in some studies could account for the wide range of prevalence.

Pain. There is a high prevalence of pain in patients with FSHD, likely up to 79%, with a low level of confidence in the evidence (1 Class II study and 2 Class III studies).[e37,e54,e55] However,

the prevalence of clinically significant pain, as reported in a single Class III study, is likely much lower at 10.8%.[e37]

Treatment.

Clinical questions.

The goal of therapy in FSHD is to improve muscle strength or function, or both. Until recently the underlying pathophysiology of FSHD was unknown, and thus pharmacologic trials have focused on improving muscle mass and strength, whereas surgical studies of scapular fixation have been motivated by efforts to improve function notwithstanding the presence of weakness. The trial of albuterol, for example, was based on animal studies showing an anabolic effect of the similar β2-agonist drug clenbuterol. Likewise, the discovery of myostatin as an inhibitor of muscle growth has generated an interest in the use of myostatin inhibitors (such as MYO-029) in the hope that these would lead to increased muscle mass and strength. In the absence of effective pharmacologic therapy, a number of strategies have been used to address the problem of weakness of scapular stabilizers, as scapular destabilization is the most prominent manifestation of the disease, affecting more than 90% of individuals.[e38] This has proven stubbornly refractory to effective bracing, providing a motivation for surgical fixation in carefully selected patients. Relevant studies that were reviewed include studies on pharmacologic interventions, exercise, and surgical scapular fixation, or a combination of these modalities. The following questions were examined:

- Do interventions (as compared with no intervention) improve patient-relevant outcomes?
- Are there features that identify patients who are more or less likely to improve with a specific intervention?

Analysis.

Pharmacologic interventions. Three Class I studies of pharmacologic interventions provided pertinent information. Two randomized, controlled trials (Class I) examined the effect of oral albuterol on strength in FSHD, in one study after 12 months of treatment and in the second study after 6 months of treatment.[e56,e57] One study showed no effect on a global measure of strength based on QMT.[e57] The other study showed a clinically unimportant increase in the strength of 7 of 12 muscles measured by QMT.[e56] A third Class I randomized, controlled study examined the effect of an IV myostatin inhibitor (MYO-029) and showed no significant improvement in muscle strength.[e58] Three additional studies of pharmacologic intervention in FSHD were excluded because all were graded Class IV. One study examined the effect of prednisone on strength, a second study examined the effect of diltiazem on strength, and a third study examined the effect of albuterol on pain and fatigue.[e59,e60,e61] All three studies showed no beneficial effect.

Surgical scapular fixation. Eleven studies were reviewed on scapular fixation surgery; one was Class III and 10 were Class IV.[e62—e72]All the studies were uncontrolled case series and involved different surgical approaches. The consistency of the response on parameters of shoulder function (forward flexion, abduction, and pain) resulted in the upgrading of the confidence in the studies from very low to low.

Exercise. Two studies provided relevant information on the role of exercise. One 52-week Class I study examined the effect of strength training on muscle strength and showed no evidence of improved isometric strength testing; however, it showed improvement of significant but questionable importance in dynamic strength in 1 of 2 muscle groups tested.[e59] A single Class III study of 8 patients with FSHD showed that 12 weeks of low-intensity aerobic exercise improved

VO$_2$ max by 16% (standard deviation [SD] 3; $p < 0.002$) and workload by 17% (SD 4; $p < 0.002$), as well as self-reported levels of activity, without evidence of muscle damage.[e73]

Conclusions.

Pharmacologic interventions. It is highly likely that albuterol is ineffective for improving muscle strength (2 Class I studies).[e56,e57] However, there is insufficient evidence to judge the efficacy of albuterol for muscle pain and fatigue (single Class IV study).[e59] The myostatin inhibitor MYO-029 is probably ineffective for improving muscle strength, pulmonary function, timed function, and QOL (single Class I study).[e58] There is insufficient evidence to support or refute the effects of prednisone (single Class IV study) or diltiazem (1 Class IV study) on muscle strength.[e60,e61]

Surgical scapular fixation. Scapular fixation is possibly effective for improving shoulder abduction and anterior flexion (1 Class III study, 9 Class IV studies) as well as shoulder pain (2 Class IV studies).[e62–e72] (The confidence in the evidence for scapular fixation was upgraded from very low to low because of the magnitude of effect.)

Exercise. On the basis of a single Class I study, strength-training exercise is probably ineffective for improving muscle strength meaningfully (1 Class I study).[e59] There is evidence that supports the use of aerobic exercise in FSHD, but the confidence in the evidence, based on a single Class III study, is very low.[e73]

PRACTICE RECOMMENDATIONS

The recommendations below encompass four major areas: diagnosis, predictors of severity, surveillance for complications, and treatment of FSHD. Each recommendation is preceded by a clinical context section that outlines the evidence, general principles of care, and evidence from related disorders that inform the recommendations.

Because of the relative paucity of literature directly relevant to FSHD, for some of the clinical questions, some of the recommendations below are based in part on evidence from other neuromuscular disorders.

Diagnosis of FSHD.

See also the algorithm in figure e-1.

Clinical context.

When clinical presentation of FSHD is typical and the inheritance pattern is consistent with autosomal dominant inheritance, clinical diagnosis is usually straightforward. If, in such circumstances, the diagnosis is genetically confirmed in a first-degree relative, genetic testing is not necessary for each affected individual. However, atypical presentations are not uncommon. In the setting of atypical or sporadic cases, genetic confirmation is important for genetic counseling, especially with the recent discovery of 2 genetically distinct forms of FSHD (PRIN). In the most common FSHD type, FSHD1, disease results from contraction of a DNA repeat sequence, termed *D4Z4 repeat*, on one copy of 4q35 from more than 10 repeats to 1 to 10 repeats. In addition, the contraction must occur in the presence of one particular (A variant) of 2 (A/B) sequence variants distal to the repeats (PRIN). Available molecular testing for FSHD1, which measures only the presence of a repeat contraction on initial testing, is highly sensitive and specific (EVID). In studies that utilized strict diagnostic criteria for FSHD, determining whether a contraction occurs on an A variant genetic background does not appear to improve diagnostic specificity (EVID). However, in clinical practice, strict clinical diagnostic criteria might not be adhered to, increasing the chances of a false-positive result (INFER). In

consequence, determining that a D4Z4 contraction is occurring on an A variant is warranted when the clinical presentation is atypical for FSHD. At present, commercial genetic testing in FSHD is limited to FSHD1 testing.

Recommendation.

A1. Clinicians should obtain genetic confirmation of FSHD1 in patients with atypical presentations and no first-degree relatives with genetic confirmation of the disease (Level B). Figure e-1 shows the recommended FSHD molecular diagnosis decision tree.

Predictors of severity in FSHD.

Clinical context.

Factors that predict disease severity in FSHD are important for counseling patients and for screening for and managing potential complications (PRIN). The D4Z4 deletion size appears to be somewhat predictive of the overall rate of disease progression (EVID). D4Z4 deletion size should be used cautiously for predicting disease progression rate in any particular individual due to other sources of variation affecting disease severity, including intrafamilial factors (INFER). Clinical experience suggests that patients with severe childhood-onset disease almost invariably have very large deletions (i.e., contracted D4Z4 allele of 10–20 kb or 1–4 repeats), suggesting a much more robust correlation between disease severity and large deletions (EVID).

Recommendation.

B1. Large D4Z4 deletion sizes (contracted D4Z4 allele of 10–20 kb) should alert the clinician that the patient is more likely to develop more significant disability and at an earlier age. Patients with large deletions are also more likely to develop symptomatic extramuscular manifestations (Level B). (See next section on monitoring for FSHD complications.).

Monitoring for complications of FSHD.

Pulmonary complications.

Clinical context. Our systematic review revealed that some patients with FSHD develop respiratory muscle weakness that can result in respiratory failure and need for mechanical ventilator assistance (e.g., nocturnal bilevel positive airway pressure), although this complication is uncommon (EVID). Patients with chronic respiratory failure from neuromuscular-related weakness often do not have classic symptoms of ventilatory failure (i.e., overt dyspnea). Impending respiratory failure, therefore, may begin with respiratory insufficiency mainly during sleep, resulting in excessive daytime somnolence or nonrestorative sleep. Respiratory insufficiency in patients with FSHD, therefore, may be evident only through pulmonary function testing (PRIN). Respiratory failure constitutes a major source of morbidity in patients with most MD types and can severely disrupt sleeping, daily activities, and QOL (PRIN). Early intervention with noninvasive mechanical ventilation leads to improved survival and QOL (RELA).[e74]

Recommendations.

C1. Clinicians should obtain baseline pulmonary function tests on all patients with FSHD. Patients should be monitored regularly if they have abnormal baseline pulmonary function test results or any combination of severe proximal weakness, kyphoscoliosis, wheelchair dependence, or comorbid conditions that may affect ventilation (e.g., chronic obstructive pulmonary disease, cardiac disease) (Level B).

C2. In patients who have FSHD and either 1) compromised pulmonary function studies (e.g., FVC <60%) or 2) symptoms of excessive daytime somnolence or nonrestorative sleep (e.g., frequent nocturnal arousals, morning headaches), clinicians should refer patients for pulmonary or sleep medicine consultation for consideration of nocturnal sleep monitoring or nocturnal noninvasive ventilation in order to improve QOL (Level B).

C3. Patients with FSHD who do not get regular pulmonary function testing should be tested prior to surgical procedures requiring general anesthesia, as such testing may uncover asymptomatic respiratory compromise (Level B).

Cardiac abnormalities.

Clinical context. Our systematic review revealed very little evidence for structural cardiac abnormalities in FSHD. Also, data are insufficient to suggest that patients with FSHD are susceptible to cardiac arrhythmias (EVID). Routine electrocardiographic or echocardiographic testing is therefore unnecessary in patients with FSHD who are asymptomatic (INFER).

Recommendation.

C4. Patients with FSHD should be referred for cardiac evaluation if they develop overt signs or symptoms of cardiac disease (e.g., shortness of breath, chest pain, palpitations). However, routine cardiac screening is not essential in the absence of cardiac signs or symptoms (Level C).

Retinal vascular disease.

Clinical context. Our systematic review suggests that symptomatic retinal vascular disease in the form of an exudative retinopathy (Coats disease) is very rare in FSHD but tends to affect patients

with large deletions almost exclusively (EVID). Untreated exudative retinopathy can lead to significant visual loss, which may be prevented by early intervention (INFER).

Recommendation.

C5. Clinicians should refer patients with FSHD and large deletions (contracted D4Z4 allele of 10–20 kb) to an experienced ophthalmologist (e.g., retina specialist) for dilated indirect ophthalmoscopy (Level B). The presence and severity of retinal vascular disease at initial screening should be used to determine the frequency of subsequent monitoring (Level B).

Hearing loss.

Clinical context. Our systematic review shows that the available studies fail to capture the prevalence and clinical relevance of hearing loss in FSHD (EVID). In clinical practice, most patients with FSHD and hearing loss requiring the use of a hearing aid have childhood-onset FSHD with large D4Z4 deletions. Two recent studies support this clinical impression (EVID). Moreover, one of the studies suggests that hearing loss is progressive in some patients. Adults and older children are cognizant of the hearing loss onset, and therefore intervention can occur early when required. However, failure to detect hearing loss in infants and younger children may significantly delay or impair language development (PRIN).

Recommendation.

C6. Clinicians should screen all young children with FSHD at diagnosis and yearly thereafter until these children start school, as hearing loss may not be present at diagnosis and can be progressive (Level B).

Pain.

Clinical context. Pain is a common complaint in FSHD and appears to be mostly musculoskeletal in origin (EVID). Pain compounding muscle weakness can have a significant impact on QOL (INFER). Physical therapists often can provide insight into the mechanism of pain in patients with weakness (PRIN). Nonsteroidal anti-inflammatory medications are useful for acute pain, and antidepressants or antiepileptics, for chronic musculoskeletal pain (PRIN).

Recommendation.

C7. Treating physicians should routinely inquire about pain in patients with FSHD. Referral for a physical therapy evaluation may prove helpful as an initial nonpharmacologic intervention. In patients with persistent pain and no contraindications, a trial of nonsteroidal anti-inflammatory medications is appropriate for acute pain and antidepressants or antiepileptics for chronic pain (Level B).

Treatment of FSHD.

Pharmacologic interventions.

Clinical context. As of this writing, no evidence exists for any effective pharmacologic interventions that improve strength or slow disease progression in FSHD. Randomized, controlled trials of albuterol were negative (EVID). Uncontrolled, open-label trials of corticosteroid and diltiazem showed no benefit. A controlled early phase II study of MYO-029, a myostatin inhibitor, also failed to show benefit.

Recommendation.

D1. In patients with FSHD, clinicians should not prescribe albuterol, corticosteroid, or diltiazem for improving strength (Level B).

Surgical scapular fixation.

Clinical context. In patients with FSHD, limited shoulder range of motion due to periscapular muscle weakness is a major source of functional limitation (PRIN). Moreover, in many patients, bedside manual scapular fixation can result in significant improvement in shoulder range of motion (PRIN). Postoperative complications are infrequent but include hemo- or pneumothorax, pain, infection, non-union, and reduced lung capacity. Scapular fixation appears to be generally safe and may be effective for improving shoulder range of motion (EVID).

Recommendation.

D2. Surgical scapular fixation might be offered cautiously to selected patients after careful consideration of the overall muscle impairment in the involved arm, assessment of potential gain in range of motion by manual fixation of the scapula, the patient's rate of disease progression, and the potential adverse consequences of surgery and prolonged postsurgical bracing (Level C).

Aerobic exercise.

Clinical context. Aerobic exercise in FSHD appears to be safe and potentially beneficial (EVID), as has been shown in many other muscle diseases (RELA).[e75] Aerobic fitness is important for overall health (PRIN). To minimize injury from falls or overuse, the type of aerobic exercise should be tailored to the patient's particular distribution of weakness. For example, a stationary bicycle rather than a treadmill should be recommended for patients with leg weakness (PRIN). Although no data exist to suggest that strength training is detrimental in FSHD (EVID), further research is needed to determine whether such strength training will result in clinically meaningful long-term functional improvement (INFER).

Recommendations.

D3. Clinicians might encourage patients with FSHD to engage in low-intensity aerobic exercise. An experienced physical therapist can help guide development of individualized exercise programs. Clinicians might also use the practical physical activities guidelines for individuals with disabilities, provided by the US Department of Health and Human Services, when counseling patients about aerobic exercise (Level C).[e76]

D4. In patients interested in strength training, clinicians may refer patients to physical therapists to establish a safe exercise program using appropriate low/medium weights/resistance that takes into consideration the patients' physical limitations (Level C).

RECOMMENDATIONS FOR FUTURE RESEARCH

- Future studies in FSHD should employ a clinical definition of disease based on consensus criteria combined with molecular genetic diagnosis.

- Observational studies (e.g., case-control and cohort) should conform to the Strengthening the Reporting of Observational Studies in Epidemiology criteria for reporting of results, leading to higher confidence in the published evidence.[e77]

- Patients with childhood-onset FSHD appear to have more severe neuromuscular manifestations as well as more clinically significant extramuscular complications. Understanding what risk factors predispose this subpopulation of patients with FSHD to such extramuscular manifestations is important for developing specific management strategies. A concerted effort is needed to study such patients with clearly defined clinical and genetic parameters.

- Use of patient registries will allow researchers to access more patients and obtain more robust data on risk factors and prognostic factors. Such a registry exists in the United States, and others are being developed elsewhere.

DISCLAIMER

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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. For complete information on this process, access the 2004 AAN process manual.[e23]
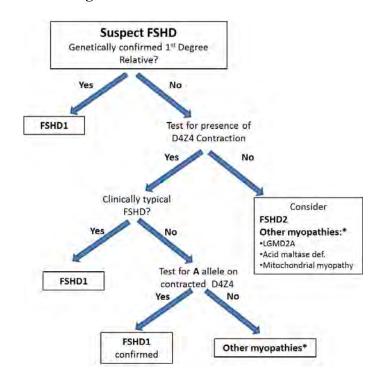
Figure e-1. Recommended diagnostic flowchart for FSHD

def. = deficiency; FSHD = facioscapulohumeral muscular dystrophy; FSHD1 = FSHD type 1;

FSHD2 = FSHD type 2; LGMD2A = limb-girdle muscular dystrophy type 2A.

Appendix e-1. AAN GDDI members and mission

The mission of the GDDI is to develop, disseminate, and implement evidence-based systematic reviews and clinical practice guidelines related to the causation, diagnosis, treatment, and prognosis of neurologic disorders.

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

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Appendix e-2. 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-3. Complete search strategy

Original Search

Executed: October 2012

Databases: Medline, EMBASE, Cochrane, and Scopus databases

Cochrane

EBM Reviews - Cochrane Central Register of Controlled Trials September 2012

#	Searches	Results	Search Type
1	Muscular Dystrophy, Facioscapulohumeral/	7	Advanced
2	facioscapul*.mp.	14	Advanced
3	1 or 2	14	Advanced
4	Muscular Dystrophies/	93	Advanced
5	(FSH or FSHD or FSHMD).mp.	1961	Advanced
6	facioscapul*.mp.	14	Advanced
7	(landouzy* adj2 dejerine*).mp.	0	Advanced
8	or/5-7	1969	Advanced
9	4 and 8	2	Advanced
10	3 or 9	14	Advanced

EBM Reviews - Cochrane Database of Systematic Reviews 2005 to August 2012

#	Searches	Results	Search Type
1	facioscapul*.mp.	10	Advanced
2	(FSH or FSHD or FSHMD).mp.	103	Advanced
3	(landouzy* adj2 dejerine*).mp.	0	Advanced
4	(muscular adj2 dystroph*).mp.	41	Advanced
5	or/1-3	106	Advanced
6	4 and 5	10	Advanced
7	1 or 6	10	Advanced

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Database of Abstracts of Reviews and Effects

EBM Reviews - Database of Abstracts of Reviews of Effects 3rd Quarter 2012

#	Searches	Results	Search Type
1	facioscapul*.mp.	0	Advanced
2	(FSH or FSHD or FSHMD).mp.	27	Advanced
3	(landouzy* adj2 dejerine*).mp.	0	Advanced
4	(muscular adj2 dystroph*).mp.	10	Advanced
5	or/1-4	37	Advanced
6	4 and 5	10	Advanced

Embase

Embase 1974 to 2012 August 27

#	Searches	Results	Search Type
1	facioscapulohumeral muscular dystrophy/	937	Advanced
2	muscular dystrophy/	13983	Advanced
3	facioscapul*.mp.	1271	Advanced
4	(landouzy* adj2 dejerine*).mp.	59	Advanced
5	(erb adj2 dystroph*).mp.	11	Advanced
6	(erb adj2 syndrome?).mp.	10	Advanced

#		Results	Search Type
7	(FSH or FSHD or FSHMD).mp.	34969	Advanced
8	or/3-7	35687	Advanced
9	2 and 8	472	Advanced
10	1 or 9	1221	Advanced
11	(exp animals/ or exp animal experimentation/) not ((exp animals/ or exp animal experimentation/) and exp human/)	2845138	Advanced
12	10 not 11	1206	Advanced
13	limit 12 to yr="2011 -Current"	138	Advanced
14	(2011* or 2012*).em.	1909158	Advanced
15	12 and 14	141	Advanced
16	13 or 15	150	Advanced

Medline

Ovid MEDLINE(R) 1946 to August Week 3 2012

#	Searches	Results	Search Type
1	Muscular Dystrophy, Facioscapulohumeral/	414	Advanced
2	Muscular Dystrophies/	12652	Advanced
3	facioscapul*.mp.	834	Advanced
4	(landouzy* adj2 dejerine*).mp.	38	Advanced
5	(FSH or FSHD or FSHMD).mp.	27736	Advanced
6	or/3-5	28110	Advanced
7	2 and 6	394	Advanced
8	1 or 7	787	Advanced
9	exp animals/ not (exp animals/ and exp humans/)	3770988	Advanced
10	8 not 9	779	Advanced
11	limit 10 to yr="2011 -Current"	58	Advanced
12	(2011* or 2012*).em.	1350055	Advanced
13	10 and 12	76	Advanced
14	11 or 13	76	Advanced

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Scopus

Limited to 2011–2012
Query:

TITLE-ABS-KEY((muscular dystroph* AND (facioscapul* OR landouzy* OR dejerine* OR (erb W/2 dystroph*) OR (erb W/2 syndrom*) OR fsh OR fshd OR fshmd))) AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal OR mult OR arts OR busi OR deci OR econ OR psyc OR soci) AND PUBYEAR > 2010 AND PUBYEAR < 2013

Search results: 125 records

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Updated Search

Executed: January 2014

Databases: Medline (via PubMed), and Cochrane

PubMed

Diagnosis/Broad[filter] AND ("muscular dystrophy, facioscapulohumeral"[MeSH Terms] OR ("muscular"[All Fields] AND "dystrophy"[All Fields] AND "facioscapulohumeral"[All Fields]) OR "facioscapulohumeral muscular dystrophy"[All Fields] OR ("fascioscapulohumeral"[All Fields] AND "muscular"[All Fields] AND "dystrophy"[All Fields]) OR "fascioscapulohumeral muscular dystrophy"[All Fields])

Therapy/Broad[filter] AND ("muscular dystrophy, facioscapulohumeral"[MeSH Terms] OR ("muscular"[All Fields] AND "dystrophy"[All Fields] AND "facioscapulohumeral"[All Fields]) OR "facioscapulohumeral muscular dystrophy"[All Fields] OR ("fascioscapulohumeral"[All

Fields] AND "muscular"[All Fields] AND "dystrophy"[All Fields]) OR "fascioscapulohumeral muscular dystrophy"[All Fields])

Appendix e-4. AAN rules for classification of evidence for risk of bias

For questions related to screening (yield)

Class I

- Study of a cohort of patients at risk for the outcome from a defined geographic area (i.e.,

population based)

- The outcome is objective

- Also required:

a. Inclusion criteria defined

b. At least 80% of patients undergo the screening of interest

Class II

- A non–population-based, nonclinical cohort (e.g., mailing list, volunteer panel) or a general

medical, neurology clinic/center without a specialized interest in the outcome. Study meets

criteria a b (see Class I)

- The outcome is objective

Class III

- A referral cohort from a center with a potential specialized interest in the outcome

Class IV

- Did not include persons at risk for the outcome

- Did not statistically sample patients, or patients specifically selected for inclusion by outcome

- Undefined or unaccepted screening procedure or outcome measure

- No measure of frequency or statistical precision calculable

For questions related to prognostic accuracy

Class I

- Cohort survey with prospective data collection

- Includes a broad spectrum of persons at risk for developing the outcome

- Outcome measurement is objective or determined without knowledge of risk factor status

- Also required:

  a. Inclusion criteria defined

  b. At least 80% of enrolled subjects have both the risk factor and outcome measured

Class II

- Cohort study with retrospective data collection or case-control study. Study meets criteria a and

  b (see Class I)

- Includes a broad spectrum of persons with and without the risk factor and the outcome

- The presence of the risk factor and outcome are determined objectively or without knowledge

  of one another

Class III

- Cohort or case-control study

- Narrow spectrum of persons with or without the disease

- The presence of the risk factor and outcome are determined objectively, without knowledge of

  the other or by different investigators

Class IV

- Did not include persons at risk for the outcome

- Did not include patients with and without the risk factor

- Undefined or unaccepted measures of risk factor or outcomes

- No measures of association or statistical precision presented or calculable

For questions related to therapeutic intervention

Class I

- Randomized, controlled clinical trial (RCT) in a representative population

- Masked or objective outcome assessment

- Relevant baseline characteristics are presented and substantially equivalent between treatment

  groups, or there is appropriate statistical adjustment for differences

- Also required:

a. Concealed allocation

b. Primary outcome(s) clearly defined

c. Exclusion/inclusion criteria clearly defined

d. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the

study) and crossovers with numbers sufficiently low to have minimal potential for bias

e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the

following are also required*:

1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority

2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective)

3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment

4. The interpretation of the study results is based on a per-protocol analysis that accounts for dropouts or crossovers

Class II

- Cohort study meeting criteria a–e above or an RCT that lacks one or two criteria b–e

- All relevant baseline characteristics are presented and substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences

- Masked or objective outcome assessment

Class III

- Controlled studies (including studies with external controls such as well-defined natural history controls)

- A description of major confounding differences between treatment groups that could affect outcome**

- Outcome assessment masked, objective, or performed by someone who is not a member of the treatment team

Class IV

- Did not include patients with the disease

- Did not include patients receiving different interventions

- Undefined or unaccepted interventions or outcome measures

- No measures of effectiveness or statistical precision presented or calculable

*Numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data)

Appendix e-5. Steps and rules for formulating recommendations

Constructing the recommendation and its rationale

Rationale for recommendation summarized in the Clinical Context includes three categories of premises

- Evidence-based conclusions for the systematic review

- Stipulated axiomatic principles of care

- Strong evidence from related conditions not systematically reviewed

Actionable recommendations include the following mandatory elements

- The patient population that is the subject of the recommendation

- The person performing the action of the recommendation statement

- The specific action to be performed

- The expected outcome to be attained

Assigning a level of obligation

Modal modifiers used to indicate the final level of obligation (LOO)

- Level A: Must

- Level B: Should

- Level C: Might

- Level U: No recommendation supported

LOO assigned by eliciting panel members' judgments regarding multiple domains, using a modified Delphi process. Goal is to attain consensus after a maximum of three rounds of voting. Consensus is defined by:

- $\geq 80\%$ agreement on dichotomous judgments

- $\geq 80\%$ agreement, within one point for ordinal judgments

- If consensus obtained, LOO assigned at the median. If not obtained, LOO assigned at the 10th percentile

Three steps used to assign final LOO

1. Initial LOO determined by the cogency of the deductive inference supporting the recommendation on the basis of ratings within four domains. Initial LOO anchored to lowest LOO supported by any domain.

   - Confidence in evidence. LOO anchored to confidence in evidence determined by modified form of the Grading of Recommendations Assessment, Development and Evaluation process[e78]

     - Level A: High confidence

     - Level B: Moderate confidence

     - Level C: Low confidence

     - Level U: Very low confidence

   - Soundness of inference assuming all premises are true. LOO anchored to proportion of panel members convinced of soundness of the inference

     - Level A: 100%

     - Level B: $\geq 80\%$ to <100%

     - Level C: $\geq 50\%$ to <80%

     - Level U or R: <50%

   - Acceptance of axiomatic principles: LOO anchored to proportion of panel members who accept principles

- Level A: 100%

- Level B: ≥80% to <100%

- Level C: ≥50% to <80%

- Level U or R: <50%

▪ Belief that evidence cited from rerated conditions is strong: LOO anchored to proportion of panel members who believe the related evidence is strong

- Level B: ≥80% to 100% (recommendations dependent on inferences from non-systematically reviewed evidence cannot be anchored to a Level A LOO)

- Level C: ≥50% to <80%

- Level U or R: <50%

2. LOO is modified mandatorily on the basis of the judged magnitude of benefit relative to harm expected to be derived from complying with the recommendation

▪ Magnitude relative to harm rated on 4-point ordinal scale

- Large benefit relative to harm: benefit judged large, harm judged none

- Moderate benefit relative to harm: benefit judged large, harm judged minimal; or benefit judged moderate, harm judged none

- Small benefit relative to harm: benefit judged large, harm judged moderate; or benefit judged moderate, harm judged minimal; or benefit judged small, harm judged none

- Benefit to harm judged too close to call: Benefit and harm judged to be the same

- Regardless of cogency of the recommendation the LOO can be no higher than that supported by the rating of the magnitude of benefit relative to harm

  - Level A: Large benefit relative to harm

  - Level B: Moderate benefit relative to harm

  - Level C: Small benefit relative to harm

  - Level U: Too close to call

- LOO can be increased by one grade if LOO corresponding to benefit relative to harm greater than LOO corresponding to the cogency of the recommendation

3. LOO optionally downgraded on the basis of the following domains

   - Importance of the outcome: critical, important, mildly important, not important

   - Expected variation in patient preferences: none, minimal, moderate, large

   - Financial burden relative to benefit expected: none, minimal, moderate, large

   - Availability of intervention: universal, usually, sometimes, limited

Appendix e-6. Clinical contextual profiles

A1. Clinicians should obtain genetic confirmation of FSHD1 in patients with atypical presentations and no first-degree relatives with genetic confirmation of the disease (Level B).

Strength of Recommendation

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

Strength of Inference

Element	Weak or N/A	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	NA
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

B1. Large D4Z4 deletion sizes (contracted D4Z4 allele of 10–20 kb) should alert the clinician that the patient is more likely to develop more significant disability and at an earlier age. Patients with large deletions are also more likely to develop symptomatic extramuscular manifestations (Level B).

Strength of Recommendation

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

Strength of Inference

Element	Weak or N/A	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	N/A
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

C1. Clinicians should obtain baseline pulmonary function tests on all patients with FSHD. Patients should be monitored regularly if they have abnormal baseline pulmonary function test

results or any combination of severe proximal weakness, kyphoscoliosis, wheelchair

dependence, or comorbid conditions that may affect ventilation (e.g., chronic obstructive

pulmonary disease, cardiac disease) (Level B).

Strength of Recommendation

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

Strength of Inference

Element	Weak or N/A	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	>50% to < 80%	>80% to < 100%	100%	N/A
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

C2. In patients who have FSHD and compromised pulmonary function studies (e.g., FVC <60%)

or symptoms of excessive daytime somnolence or nonrestorative sleep (e.g., frequent nocturnal

arousals, morning headaches), clinicians should refer for pulmonary or sleep medicine

consultation for consideration of nocturnal sleep monitoring or nocturnal noninvasive ventilation

in order to improve QOL (Level B).

Strength of Recommendation

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

Strength of Inference

Element	Weak or N/A	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	>50% to < 80%	>80% to < 100%	100%	N/A
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

C3. Patients with FSHD who do not get regular pulmonary function testing should be tested prior to surgical procedures requiring general anesthesia, as such testing may uncover asymptomatic respiratory compromise (Level B).

Strength of Recommendation

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

Strength of Inference

Element	Weak or N/A	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	>50% to < 80%	>80% to < 100%	100%	N/A
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

C4. Patients with FSHD should be referred for cardiac evaluation if they develop overt signs or symptoms of cardiac disease (e.g., shortness of breath, chest pain, palpitations). However, routine cardiac screening is not essential in the absence of cardiac signs or symptoms (Level C).

Strength of Recommendation

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

Strength of Inference

Element	Weak or N/A	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	NA
Acceptance of Principles	<50%	>50% to < 80%	>80% to < 100%	100%	N/A
Logical	<50%	>50% to < 80%	> 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

C5. Clinicians should refer patients with FSHD and large deletions (contracted D4Z4 allele of 10–20 kb) to an experienced ophthalmologist (e.g., retina specialist) for dilated indirect ophthalmoscopy (Level B). The presence and severity of retinal vascular disease at initial screening should be used to determine the frequency of subsequent monitoring (Level B).

Strength of Recommendation

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

Strength of Inference

Element	Weak or N/A	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	NA
Acceptance of Principles	<50%	>50% to < 80%	>80% to < 100%	100%	N/A
Logical	<50%	>50% to < 80%	> 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

C6. Clinicians should screen all young children with FSHD at diagnosis and yearly thereafter until these children start school, as hearing loss may not be present at diagnosis and can be progressive (Level B).

Strength of Recommendation

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

Strength of Inference

Element	Weak or N/A	Modest	Moderate	Strong	Consensus
Internal inferences	<50%	>50% to < 80%	>80% to < 100%	100%	N/A
Strong related evidence	<50%	>50% to < 80%	>80% to 100%	X	NA
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

C7. Treating physicians should routinely inquire about pain in patients with FSHD. Referral for a physical therapy evaluation may prove helpful as an initial nonpharmacologic intervention. In patients with persistent pain and no contraindications, a trial of nonsteroidal anti-inflammatory medications is appropriate for acute pain and antidepressants or antiepileptics for chronic pain (Level B).

Strength of Recommendation

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

Strength of Inference

Element	Weak or N/A	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	NA
Acceptance of Principles	<50%	>50% to < 80%	>80% to < 100%	100%	N/A
Logical	<50%	>50% to < 80%	> 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

D1. In patients with FSHD, clinicians should not prescribe albuterol, corticosteroid, or diltiazem for improving strength (Level B).

Strength of Recommendation

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

Strength of Inference

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

The author panel judged that even for therapies with only Class IV evidence, the known side effects (e.g., steroids) affected the risk–benefit tradeoff in such a way as to warrant a recommendation against use.

D2. Surgical scapular fixation might be offered cautiously to selected patients after careful consideration of the overall muscle impairment in the involved arm, assessment of potential gain

in range of motion by manual fixation of the scapula, the patient's rate of disease progression, and the potential adverse consequences of surgery and prolonged postsurgical bracing (Level C).

Strength of Recommendation

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

Strength of Inference

Element	Weak or N/A	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	N/A
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

D3. Clinicians might encourage patients with FSHD to engage in low-intensity aerobic exercise. An experienced physical therapist can help guide development of individualized exercise programs. Clinicians might also use the practical physical activities guidelines for individuals with disabilities, provided by the US Department of Health and Human Services, when counseling patients about aerobic exercise (Level C).[e76]

Strength of Recommendation

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

Strength of Inference

Element	Weak or N/A	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	N/A
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

D4. In patients interested in strength training, clinicians may refer patients to physical therapists to establish a safe exercise program using appropriate low/medium weights/resistance that takes into consideration the patients' physical limitations (Level C).

Strength of Recommendation

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

Strength of Inference

Element	Weak or N/A	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	N/A
Acceptance of Principles	<50%	>50% to < 80%	>80% to < 100%	100%	N/A
Logical	<50%	>50% to < 80%	> 80% to < 100%	100%	Yes
Confidence in Evidence	Very Low	Low	Moderate	High	Yes

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