Summary of Evidence-based Guideline for **CLINICIANS**

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

This is a summary of the American Academy of Neurology and American Association of Neuromuscular & Electrodiagnostic Medicine guideline on the diagnosis and treatment of limb-girdle muscular dystrophies (LGMD) and distal muscular dystrophies. The terms *LGMD* and *muscular dystrophy* are used interchangeably to refer to the disorders reviewed in this guideline.

Please refer to the full guideline at AAN.com/guidelines for more information, including the complete set of recommendations, complete clinical context, and definitions of the classifications of evidence and recommendations.

SCREENING AND DIAGNOSIS

What is the frequency of genetically confirmed LGMD subtypes?

Clinical Context

Most LGMDs are rare, with estimated prevalences ranging from 0.07 (LGMD2D and LGMD2E) to 0.43 (LGMD2I) per 100,000. The most common adult-onset muscular dystrophies presenting with limb-girdle weakness are Becker muscular dystrophy (BMD) (dystrophin), LGMD2A (calpain 3), LGMD2I (fukutin-related protein), and LGMD2L (anoctamin 5), whereas the most common distal myopathy is Miyoshi myopathy (dysferlin and anoctamin 5).

How often do patients with muscular dystrophy and its specific subtypes have specific clinical features, including ethnic predilection, diagnostic patterns of weakness, respiratory and cardiac complications, laboratory abnormalities (e.g., elevated creatine kinase), specific patterns on imaging, and muscle biopsy features?

Clinical Context

There are some features common to most LGMDs. Patients typically present with slowly progressing symmetrical weakness. The age at onset is usually adolescence to early adulthood but is highly variable, ranging from early childhood to late adult life. Limb-girdle weakness affecting proximal muscles of the arms and legs is the most common pattern. Other patterns include scapuloperoneal weakness and distal weakness. A single genotype can present with different phenotypes. Conversely, a single phenotype can result from more than one genotype.

There are some features that help to differentiate specific types of LGMD or at least narrow the differential diagnosis. Some distinguishing clinical characteristics of many LGMD disorders include the following:

- Early development of foot drop (e.g., myofibrillar myopathies [MFM])
- Asymmetry in muscle weakness (e.g., LGMD1A, LGMD2L, MFM)
- Limb contractures (lamin A/C myopathies, Emery-Dreifuss muscular dystrophy [EDMD], *BAG3*)
- Prominent muscle cramps (LGMD1C)
- Ancestry (e.g., northern European for LGMD2I)
- Family or personal history of frontotemporal dementia, Paget disease of bone, or motor neuron disease (h1BMPFD)
- Scapular winging (e.g., sarcoglycanopathies, LGMD2A)
- Calf hypertrophy (BMD, LGMD2I)
- Cardiac conduction system abnormalities (e.g., laminopathy, desminopathy)
- Cardiomyopathy (e.g., LGMD2I)

These features for the major LGMD disorders are presented in table 1 (also available online as table e-2, a data supplement to the published guideline).

Some LGMD subtypes may present with other characteristics, such as rippling muscle phenomenon and percussion-induced muscle contractions in LGMD1C or distinguishing EMG features in MFM (e.g., myotonic and pseudomyotonic discharges, the latter characterized by runs of decrescendo positive sharp wave discharges without the typical waxing and waning of amplitudes and frequencies).

Muscle biopsy features that can distinguish muscular dystrophies include the presence of rimmed vacuoles, reducing bodies/cytoplasmic bodies, and derangement of myofibrils consistent with MFM. Nemaline rods may be seen in distal myopathies due to nebulin mutations. Reductions of specific proteins on immunohistochemistry suggest deficiencies of these proteins, although the diagnosis needs to be confirmed by genetic testing.

Level B	For patients with suspected muscular dystrophy, clinicians should use a clinical approach to guide genetic diagnosis based on the clinical phenotype, including the pattern of muscle involvement, inheritance pattern, and associated manifestations (e.g., early contractures, cardiac or respiratory involvement).
Level C	In patients with suspected muscular dystrophy in whom initial clinically directed genetic testing does 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.

TREATMENT

Are there effective therapies for muscular dystrophies?

EVALUATION AND MEDICAL MANAGEMENT OF MUSCULAR DYSTROPHIES

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).

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

Clinical Context: Cardiac Involvement

The detection and appropriate management of cardiac dysfunction are important to reduce morbidity and mortality (PRIN). LGMD subtypes with associated cardiac involvement include: LGMD1A, LGMD1B, LGMD1D, LGMD1E, LGMD2C–K, LGMD2M–P, BMD, EDMD, and MFM. 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).

Level B	Clinicians should refer 1) newly diagnosed patients with LGMD1A, LGMD1B, LGMD1D, LGMD1E, LGMD2C–K, LGMD2M–P, BMD, EDMD, and MFM and 2) muscular dystrophy patients 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.
	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.
	Clinicians should refer muscular dystrophy patients with palpitations, symptomatic or asymptomatic tachycardia or arrhythmias, or signs or symptoms of cardiac failure for cardiology evaluation.
	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.

Clinical Context: Dysphagia and Nutrition

Patients with muscular dystrophy may have difficulty receiving adequate oral intake due to dysphagia and/or inability to feed themselves due to 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 (e.g., gastrostomy or jejunostomy feeding tubes) may be needed to maintain optimal nutrition (PRIN).

Level B	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.

Clinical Context: Pulmonary Complications

Some forms of muscular dystrophy (e.g., LGMD2I or MFM) are associated with oropharyngeal or ventilatory muscle weakness. Patients with these forms are at high risk for developing respiratory failure during the course of their disease. Patients with other forms of muscular dystrophy (e.g., 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). Patients with respiratory failure secondary to muscle weakness often have improved quality of life with noninvasive pulmonary ventilation (RELA).

Level B	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.
	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.
	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 C	It is not obligatory for clinicians to refer patients with LGMD2B and LGMD2L for pulmonary evaluation unless they are symptomatic.

Clinical Context: Spinal Deformities

Musculoskeletal spine deformities, such as scoliosis, kyphosis, or rigid spine syndrome, can result in discomfort and functional impairment, interfering with gait, activities of daily living, and pulmonary function (PRIN). Their management is important in order to reduce discomfort, preserve mobility or ability to sit in a wheelchair, and reduce pulmonary complications (RELA).

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

Clinical Context: Osteoporosis

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).

Level C	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.

Clinical Context: Infection Prophylaxis

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). 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).[1] 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).

Level B	Clinicians should recommend PPSV23 as per the CDC schedule[1] and annual influenza vaccine to patients with muscular dystrophy in order to prevent respiratory complications of pneumococcal pneumonia and influenza.

REHABILITATIVE MANAGEMENT AND TREATMENT OF MUSCULAR DYSTROPHIES

Clinical Context: Clinical Rehabilitative Management

The currently available data are not adequate to assess the effect of any rehabilitation modality (endurance and strength training, bracing, and assistive devices, including new computer-based technology) (EVID). However, the principles of long-term management 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. Another important aspect of management includes proactively preparing patients and their families for the long-term consequences of muscular dystrophies and engaging in discussions regarding end-of-life care.

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

Clinical Context: Strength Training and Aerobic Exercise

Evidence regarding the effectiveness of rehabilitation management in muscular dystrophies is limited. However, the available evidence suggests that this population would benefit from strengthening and aerobic fitness training programs. Due to the muscle degeneration in muscular dystrophy, there may be some risk of exercise-induced muscle damage, myoglobinuria, and subsequent overwork weakness following supramaximal, high-intensity exercise. 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). On the basis of this literature, both strength training and aerobic exercise programs appear to be safe, without any notable deleterious effects.

Level B	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 C	Clinicians may advise patients with muscular dystrophy that aerobic exercise combined with a supervised submaximal strength training program is probably safe.
	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.
	Clinicians may counsel patients with muscular dystrophy to hydrate adequately, not to exercise to exhaustion, and to avoid supramaximal, high-intensity exercise.

Clinical Context: Medical Treatments

The systematic review demonstrated that effects on the clinical course and the long-term safety of gene transfer, myoblast transplantation, neutralizing antibody to myostatin, or growth hormone are yet to be determined.

Level R	Clinicians should not currently offer patients with muscular dystrophy gene therapy, myoblast transplantation, neutralizing antibody to myostatin, or growth hormone outside of a research study designed to determine the efficacy and safety of the treatment.

For conceptual and diagnostic algorithms for LGMD diagnosis, see figures 1 through 7 below (also available as figures 1 through 5 in the published guideline and figures e-1 and e-2, online data supplements to the published guideline).

Table 1. Distinguishing features of muscular dystrophies

Designation	Protein	Chromosome	Inheritance	Common patterns of weakness	Distinguishing clinical features	Distinguishing EMG and muscle biopsy features	Complications
X-linked muscular dystrophies							
EDMD-X1	Emerin	Xq28	XR	HP	Contractures invariably present early in the disease course		Cardiac conduction abnormalities
EDMD-X2	FHL1	Xq27.2	XR	LG, HP or SP, DM	Foot drop; extremity contractures and neck contractures common	Myofibrillar myopathy or reducing bodies	Severe respiratory failure in many patients
Becker muscular dystrophy	Dystrophin	Xp21	XR	LG	Calf hypertrophy	Mosaic appearance of dystrophin on immunohistochemistry in affected woman	Dilated cardiomyopathy in 4% to 70% depending on disease duration
Limb-girdle muscular dystrophies (LGMDs)							
LGMD1A	Myotilin	5q22.3-31.3	AD	LG, DM	Onset > 40 years, foot drop, asymmetric muscle weakness and atrophy	Myofibrillar myopathy, myotonic or pseudomyotonic discharges	Cardiomyopathy, respiratory muscle weakness
LGMD1B	Lamin A/C	1q11-21	AD	LG, HP, DM	Early humeroperoneal weakness, limb contractures		Cardiomyopathy and conduction system disease
LGMD1C	Caveolin-3	3p25	AD	LG	Rippling muscles, percussion-induced rapid contractions, prominent muscle cramps and calf hypertrophy		
LGMD1D	DNAJB6	6q23	AD	LG, DM	Onset > 40 years, foot drop	Myofibrillar myopathy, rimmed vacuoles, myotonic or pseudomyotonic discharges	
LGMD1E	Desmin	2q35	AD	LG, HP, DM	Onset < 40 years, foot drop	Myofibrillar myopathy, myotonic or pseudomyotonic discharges	Cardiomyopathy, respiratory muscle weakness
LGMD2A	Calpain-3	15q15.1-21.1	AR	LG	More common in patients with British, Southern or Eastern European, or Brazilian ancestry; scapular winging; absence of calf hypertrophy	Inflammatory changes on some biopsies	
LGMD2B	Dysferlin	2p13	AR	LG, DM (Miyoshi phenotype)	Calf atrophy, inability to stand on toes		Left ventricular hypertrophy or reduced ejection fraction in rare patients

Designation	Protein	Chromosome	Inheritance	Common patterns of weakness	Distinguishing clinical features	Distinguishing EMG and muscle biopsy features	Complications
Limb-girdle muscular dystrophies (LGMDs)							
LGMD2C	γ-Sarcoglycan	13q12	AR	LG	Age of onset 2 to 23 years; macroglossia, ankle contractures, and scoliosis		Severe ventilatory muscle weakness has been reported in up to one-third of patients
LGMD2D	α-Sarcoglycan	17q12-21.3	AR	LG			
LGMD2E	β-Sarcoglycan	4q12	AR	LG			
LGMD2F	δ-Sarcoglycan	5q33-34	AR	LG	Early age of onset, 4 to 10 years		Early respiratory muscle involvement
LGMD2G	Telethonin	17q11-12	AR	LG		Rimmed vacuoles	Cardiac involvement, type unspecified
LGMD2H	E3-ubiquitin-ligase (TRIM32)	9q31-33	AR		Hutterite descent	Many small vacuoles usually more prominent in type II fibers	
LGMD2I	Fukutin-related protein (FKRP)	19q13	AR	LG	Northern European ancestry, scapular winging, calf hypertrophy, early cardiorespiratory involvement		Dilated cardiomyopathy and respiratory dysfunction common
LGMD2J	Titin	2q31	AR	LG	Finnish and French populations	Rimmed vacuoles	
LGMD2K	POMT1	9q31	AR	LG			
LGMD2L	Anoctamin-5	11p14.3	AR	LG, DM (Miyoshi phenotype)	Calf atrophy, inability to stand on toes		
LGMD2M (fukutin)	Fukutin	9q31-33	AR		Early age of onset, 4 months to 4 years		Some muscle biopsies with prominent inflammatory changes
LGMD2N	POMT2	14q24	AR	LG			
LGMD2O	POMGNT1	1p32	AR	LG			
LGMD2P	α-Dystroglycan	3p21	AR	LG			
LGMD2Q	Plectin	8q24.3	AR	LG	History of epidermolysis bullosa; pyloric atresia seen in other forms of plectinopathies, although not in LGMD2Q		
Myofibrillar myopathies							
Myotilinopathy (LGMD1A)	Myotilin	5q22.3-31.3	AD	LG, DM	Onset > 40 years, foot drop, asymmetric muscle weakness and atrophy	Myofibrillar myopathy, myotonic or pseudomyotonic discharges	Cardiomyopathy, respiratory muscle weakness
Desminopathy (LGMD1E)	Desmin	2q35	AD	LG, HP, DM	Onset < 40 years, foot drop	Myofibrillar myopathy, myotonic or pseudomyotonic discharges	Cardiomyopathy, respiratory muscle weakness

Designation	Protein	Chromosome	Inheritance	Common patterns of weakness	Distinguishing clinical features	Distinguishing EMG and muscle biopsy features	Complications
Myofibrillar myopathies							
Titinopathy (HMERF)	Titin	2q31	AD	LG	Finnish and French populations	Rimmed vacuoles, myofibrillar myopathy	Autosomal dominant, early respiratory failure
BAG3	BCL2-associated athanogene 3	10q25.2-q26.2	AD	LG, DM	Onset < 40 years, foot drop	Myofibrillar myopathy, myotonic or pseudomyotonic discharges	Cardiomyopathy, respiratory muscle weakness
Filamin C (Williams distal myopathy)	Filamin C	7q32.1	AD	LG, DM	Onset > 40 years, foot drop	Myofibrillar myopathy, myotonic or pseudomyotonic discharges	Cardiomyopathy, respiratory muscle weakness
αB-Crystallin	αB-Crystallin	11q21-23	AD	LG, DM	Early or late onset, foot drop	Myofibrillar myopathy, myotonic or pseudomyotonic discharges	Cardiomyopathy, respiratory muscle weakness
ZASP	Z-band alternatively spliced PDZ motif-containing protein	10q22.3-23.2	AD	LG, DM	Onset > 40 years, foot drop	Myofibrillar myopathy, myotonic or pseudomyotonic discharges	Cardiomyopathy, respiratory muscle weakness
FHL1	Four-and-one-half LIM1 protein	Xq27.2	X-linked	LG, HP or SP, DM	Foot drop; extremity contractures and neck contractures common	Myofibrillar myopathy or reducing bodies	Severe respiratory failure in many patients
Hereditary inclusion body myopathy (hIBM)							
AR hIBM	Glucosamine (UDP-N-acetyl)-2-epimerase/ N-acetylmanno-samine kinase (GNE)		AR	DM	Early adult onset, foot drop	Rimmed vacuoles	
AD hIBMPFD	Valosin-containing protein (VCP)		AD	LG, DM	Proximal and distal weakness; past or family history of frontotemporal dementia, Paget disease, motor neuron disease	Rimmed vacuoles, myotonic discharges	
hIBM3	MYHC-IIA		AD	LG	External ophthalmoplegia, joint contractures	Rimmed vacuoles, lobulated fibers, absent type IIA fibers	
Distal dystrophies/myopathies							
Welander distal myopathy	TIA1	2p13	AD	DM	Swedish/Finnish ancestry, late adult onset, index finger and wrist extensor weakness followed by atrophy of hand muscles		

Designation	Protein	Chromosome	Inheritance	Common patterns of weakness	Distinguishing clinical features	Distinguishing EMG and muscle biopsy features	Complications
Distal dystrophies/myopathies							
Udd distal myopathy	Titin	2q31	AR, AD	LG, DM			Some phenotypes with early respiratory failure or early dilated cardiomyopathy
Markesbery-Griggs	Z-band alternatively spliced PDZ motif-containing protein (ZASP)	10q22.3-23.2	AD	LG, DM	Onset > 40 years, foot drop	Myofibrillar myopathy, myotonic or pseudomyotonic discharges	Cardiomyopathy, respiratory muscle weakness
Laing, hyaline body myopathy	MYH7, myosin heavy chain	14q11	AD	DM	Early adult onset, foot drop, neck weakness, disabling myalgias, calf hypertrophy		Cardiomyopathy
Williams distal myopathy	Filamin C	7q32.1	AD	LG, DM	Onset > 40 years, foot drop	Myofibrillar myopathy, myotonic or pseudomyotonic discharges	Cardiomyopathy, respiratory muscle weakness
Vocal cord and pharyngeal weakness with distal myopathy (VCPDM)	Matrin-3	5q31.2	AD	DM	Mean age at onset 45 years, foot drop and distal upper extremity weakness, dysphagia, dysphonia	Subsarcolemmal rimmed vacuoles	
Distal myopathy with Kelch-like homologue 9 mutations	Kelch-like 9	9p22	AD	DM			
Miyoshi myopathy type I, LGMD2B	Dysferlin	2p13	AR	DM (Miyoshi phenotype)	Calf atrophy, inability to stand on toes		Left ventricular hypertrophy or reduced ejection fraction in rare patients
Miyoshi myopathy type III, LGMD2L	Anoctamin-5	11p14.3	AR	DM (Miyoshi phenotype)	Calf atrophy, inability to stand on toes		
Nonaka myopathy, AR hIBM	Glucosamine (UDP-N-acetyl)-2-epimerase/ N-acetylmanno-samine kinase (GNE)		AR	DM	Early adult onset, foot drop	Rimmed vacuoles	
Nebulin myopathy	Nebulin	2q21.2-q22	AR	DM	Early adult onset, foot drop	Nemaline rods	

Designation	Protein	Chromosome	Inheritance	Common patterns of weakness	Distinguishing clinical features	Distinguishing EMG and muscle biopsy features	Complications
Other dystrophies							
Bethlem myopathy	Collagen VI		AD	HP	Joint laxity, prominent calcanei, variable age of onset		
Ullrich myopathy	Collagen VI		AR	HP	Joint laxity, prominent calcanei, neonatal or congenital onset		
Selenoprotein N1 (rigid spine syndrome)*	Selenoprotein N1	1p36	AR	LG	Rigid spine, joint contractures, generalized weakness	Multiminicores, cores, Mallory bodies, type I fiber predominance	Restrictive lung disease
Muscular dystrophy with generalized lipodystrophy	Cavin-1/PTRF	17q21.2	AR	Distal dominant, generalized	Generalized lipodystrophy, myalgia, cramps, percussion-induced muscle mounding, hepatosplenomegaly, insulin resistance, acanthosis nigricans		Arrhythmias including prolonged QT syndrome, sudden cardiac death

Abbreviations: AD = autosomal dominant; AR = autosomal recessive; DM = distal muscular; EDMD = Emery-Dreifuss muscular dystrophy; hIBMPFD = hIBM with Paget disease and frontotemporal dementia; HMERF = hereditary myopathy with early respiratory failure; HP = humeroperoneal; LG = limb-girdle; PTRF = polymerase I and transcript release factor; SP = scapuloperoneal; XR = X-linked recessive

*Rigid spine syndrome can also be caused by FHL1, BAG3, lamin A/C, and collagen VI mutations.

LGMD 2R and 2S were described after this systematic review was performed and hence are not discussed in this guideline.

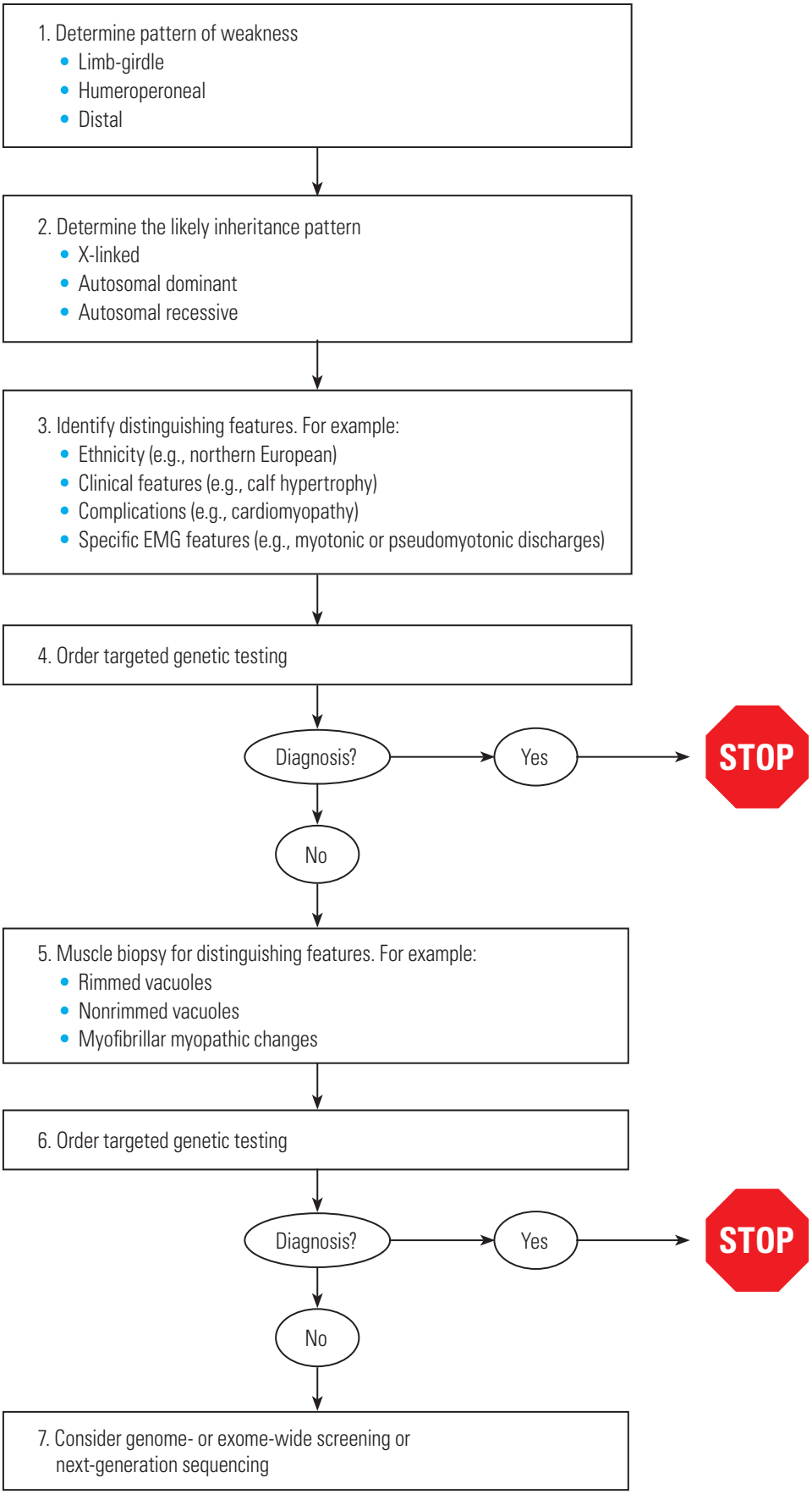

Figure 1. Conceptual approach to a patient with a suspected limb-girdle muscular dystrophy

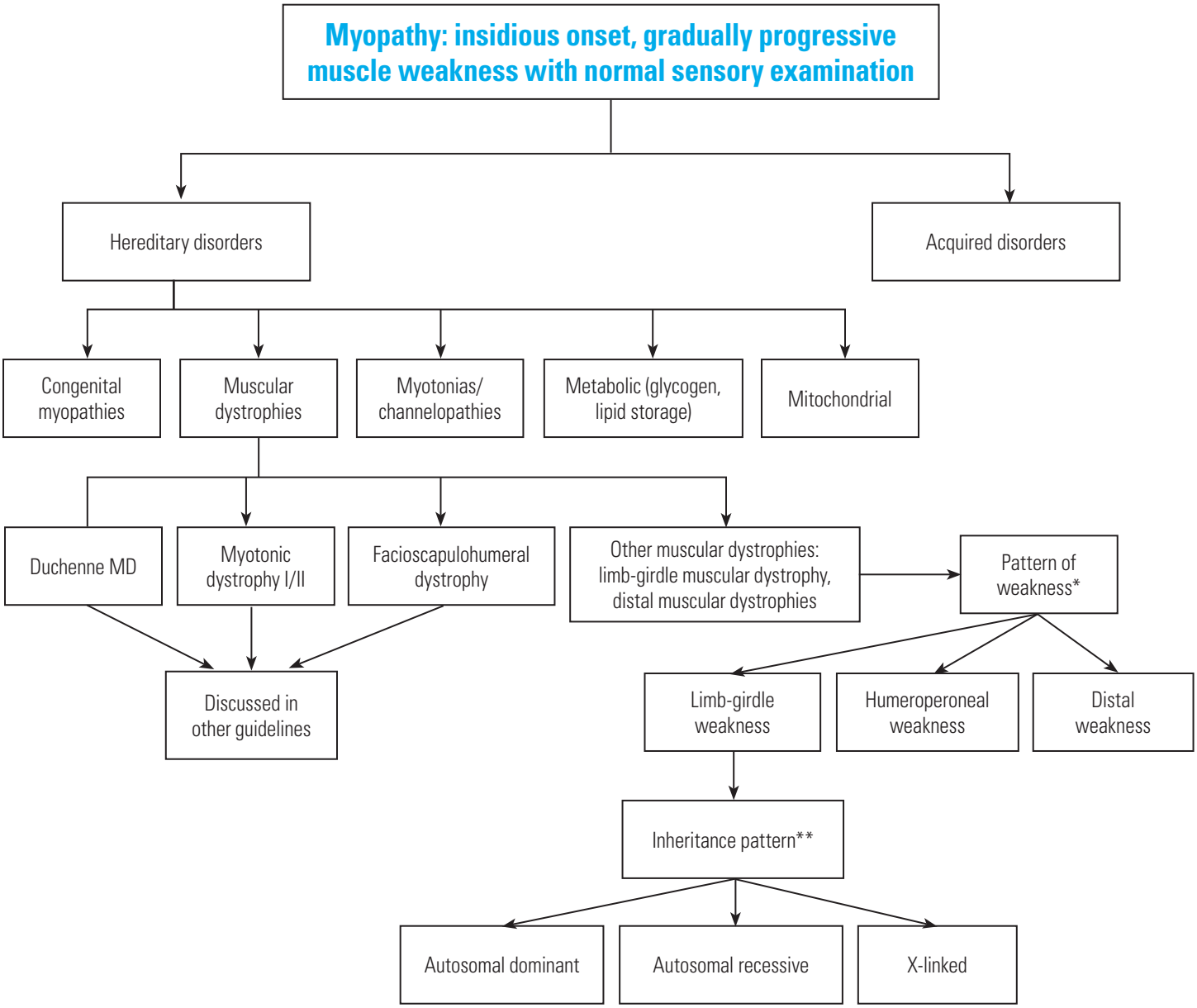

Figure 2. General classification of myopathies

The differential diagnosis of myopathy includes several diverse conditions, both inherited and acquired. The neuromuscular examination, ancillary laboratory tests, and EMG assist in the differential diagnosis of these disorders. The term "other muscular dystrophies" is used here to indicate hereditary disorders of muscle that have 3 major phenotypes of weakness: limb-girdle, humeroperoneal, and distal.

*Other muscular dystrophy phenotypes. Limb-girdle pattern of weakness: symmetric weakness predominantly affecting the proximal legs and arms. Distal muscles may be involved but to a much lesser extent. Neck flexors and extensors may be involved. Humeroperoneal: humeral muscles (biceps and triceps) and the anterior compartment of the distal leg muscles. May be asymmetric. Distal: weakness involving the anterior or posterior compartments of the distal legs or the distal arm/forearm muscles. Other patterns, such as distal arm/proximal leg (inclusion body myositis), ptosis/ophthalmoplegia (myasthenia gravis, myotonic dystrophy, some congenital myopathies, oculopharyngeal muscular dystrophy, mitochondrial myopathy), and neck extensor weakness ("dropped head syndrome," amyotrophic lateral sclerosis, myasthenia gravis, inflammatory myopathies, isolated neck extensor myopathy), may be noted and suggest specific diagnoses other than limb-girdle muscular dystrophy and variants, as noted in parentheses.

**Autosomal dominant, autosomal recessive, or X-linked inheritance may be responsible in sporadic cases.

Figures 3–7 discuss the clinical approach to diagnosis using the inheritance pattern and the pattern of weakness (as outlined in figure 2) as a starting point.

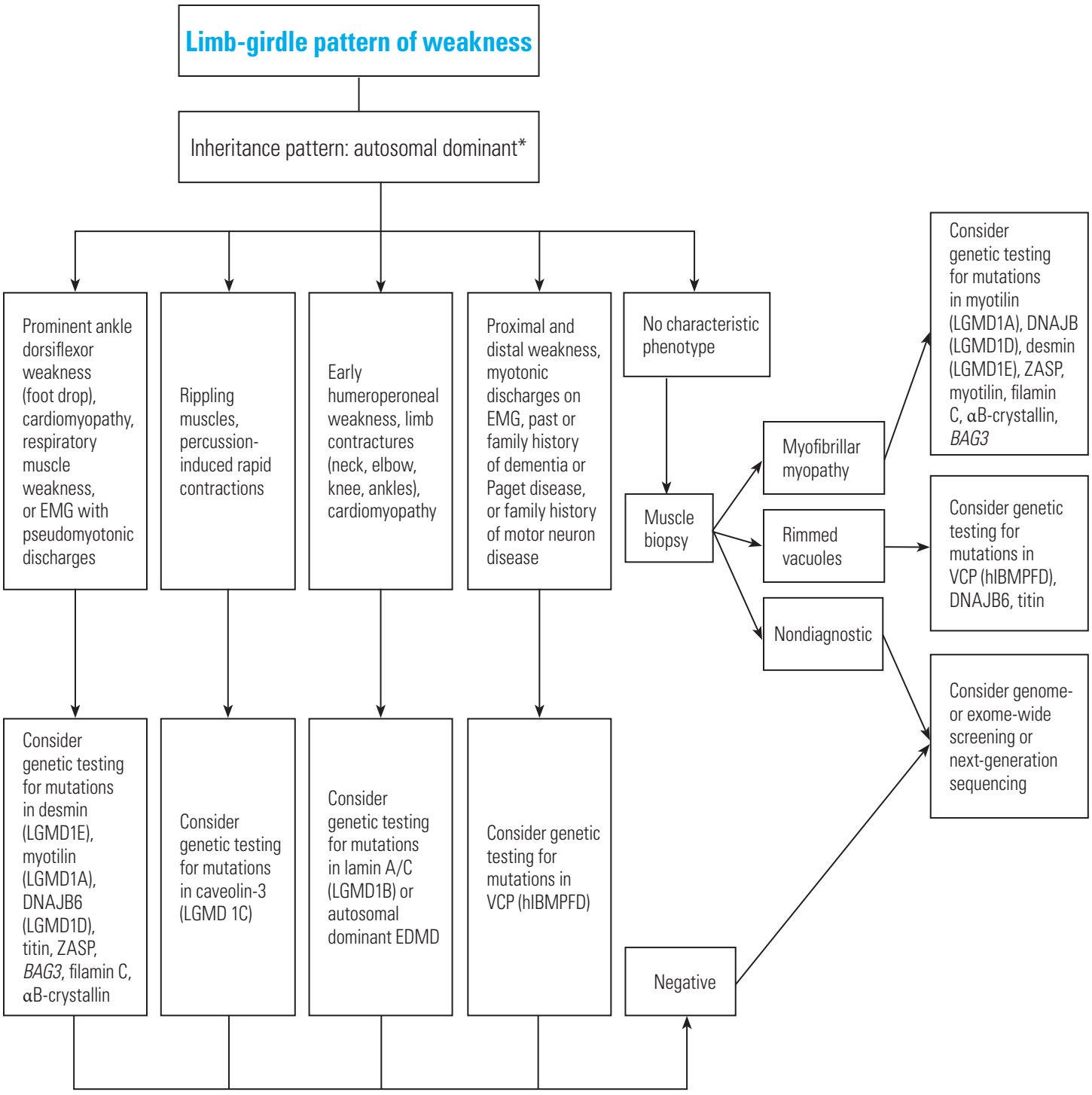

Figure 3. Diagnostic approach to patients with a limb-girdle pattern of weakness and suspected muscular dystrophy with an autosomal dominant inheritance pattern

*Autosomal dominant, autosomal recessive, or X-linked inheritance may be responsible in sporadic cases.

EDMD = Emery-Dreifuss muscular dystrophy; hIBMPFD = hereditary inclusion body myopathy with Paget disease and frontotemporal dementia; LGMD = limb-girdle muscular dystrophy; VCP = valosin-containing protein.

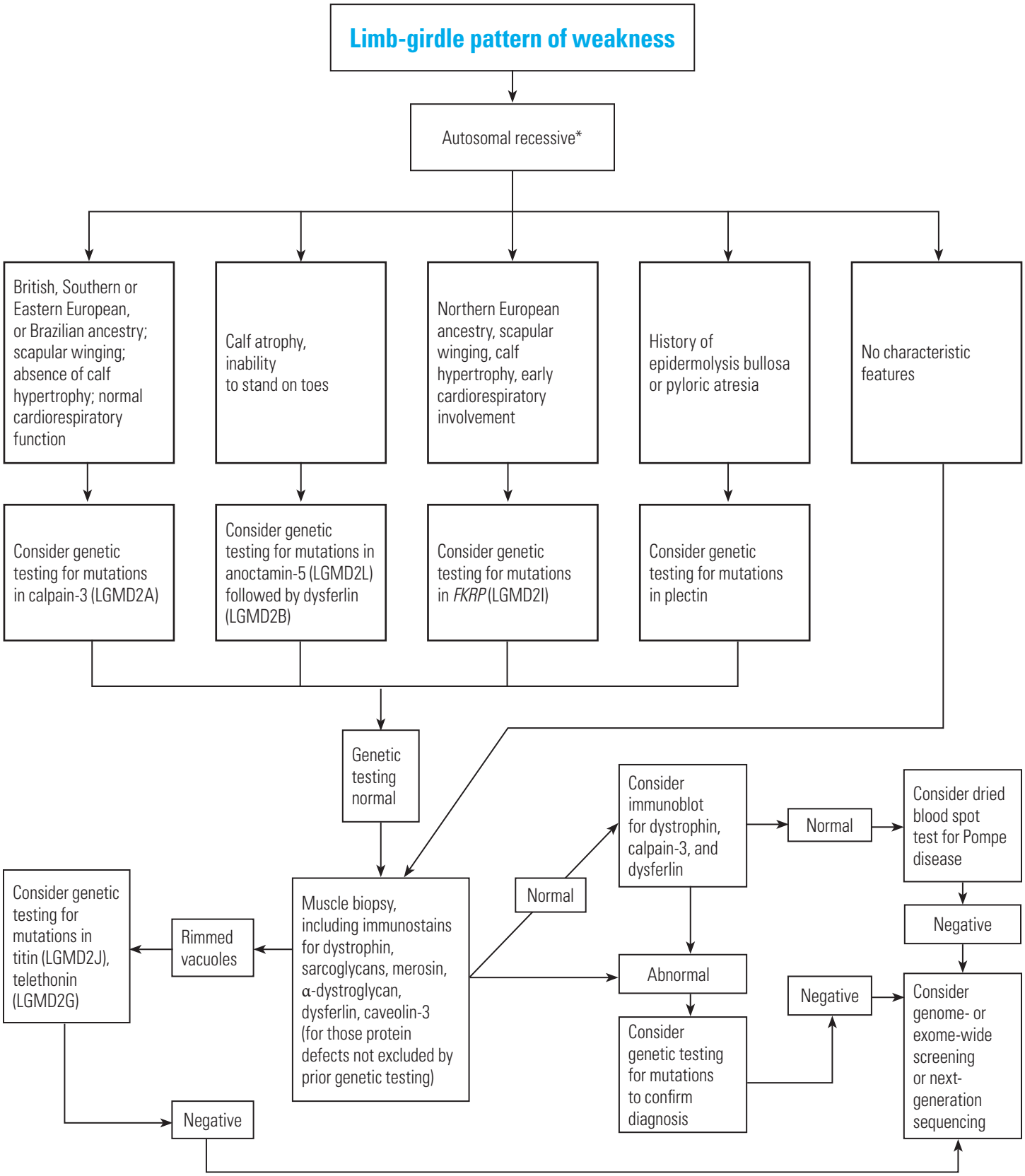

Figure 4. Diagnostic approach to patients with a limb-girdle pattern of weakness and suspected muscular dystrophy with an autosomal recessive inheritance pattern

*Autosomal dominant, autosomal recessive, or X-linked inheritance may be responsible in sporadic cases.

LGMD = limb-girdle muscular dystrophy.

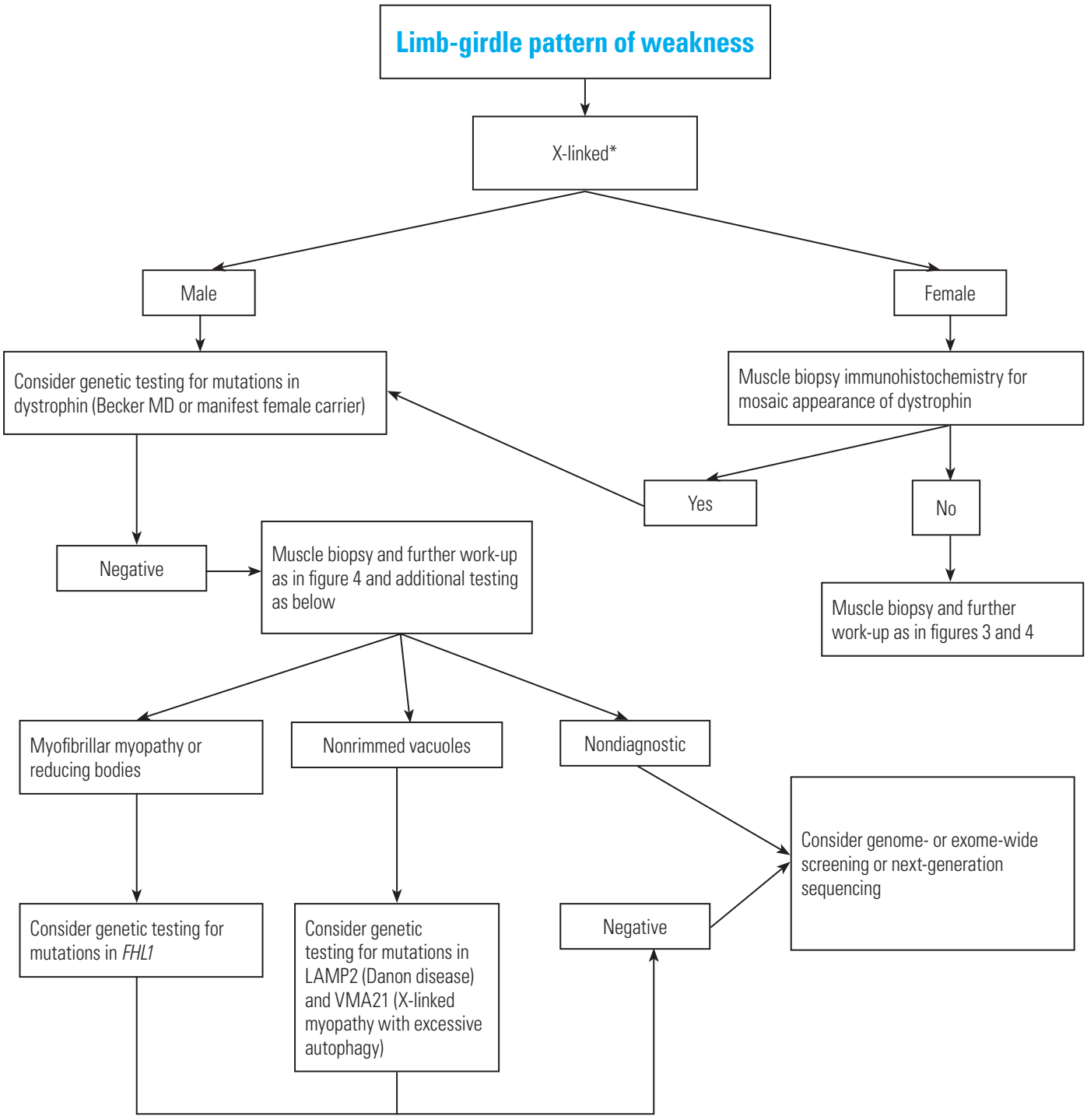

Figure 5. Diagnostic approach to patients with a limb-girdle pattern of weakness and suspected muscular dystrophy with an X-linked recessive inheritance pattern

In females, a manifest X-linked disorder may be considered if there is a familial presentation with males more affected than females.

*Autosomal dominant, autosomal recessive, or X-linked inheritance may be responsible in sporadic cases.

MD = muscular dystrophy.

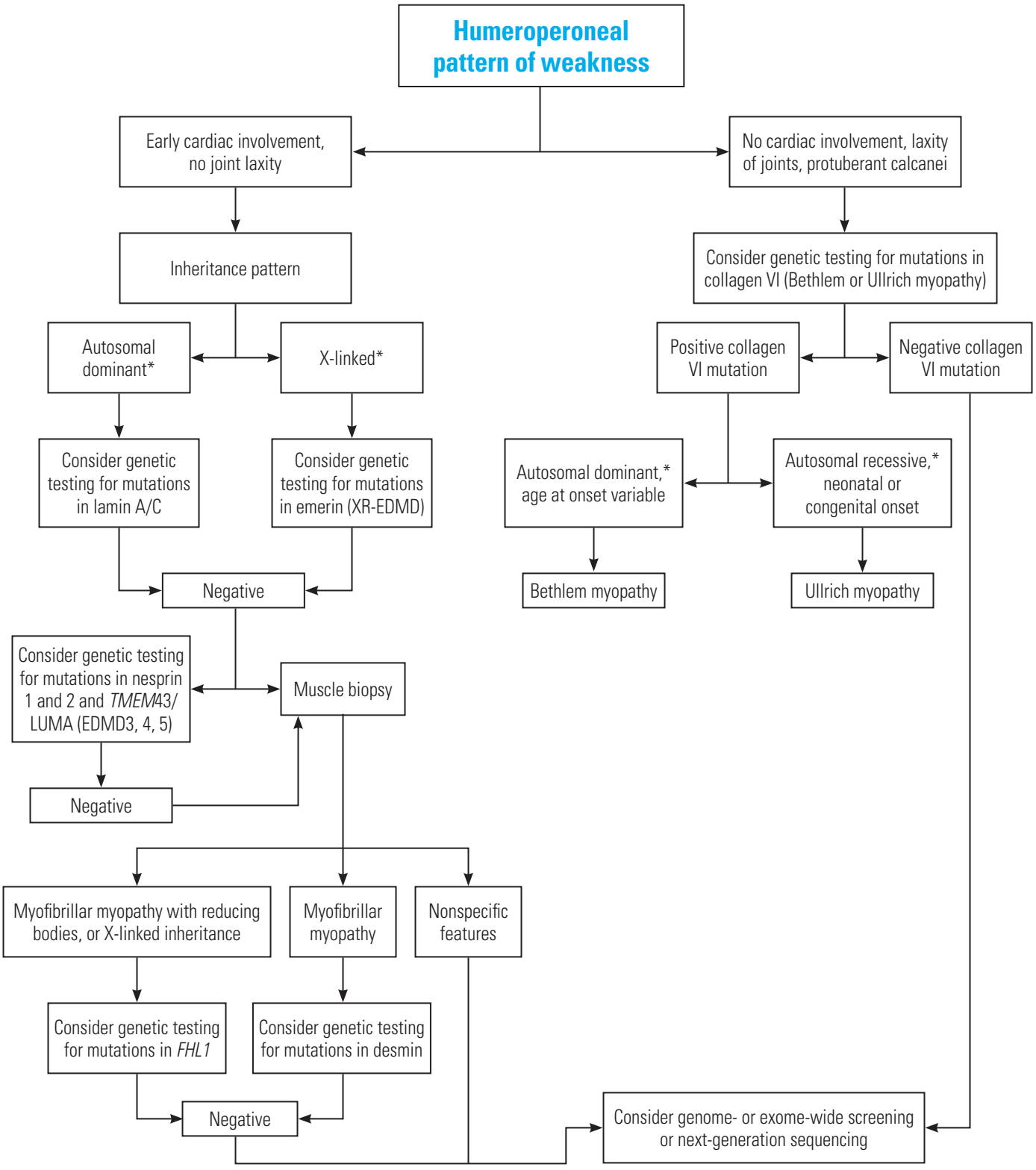

Figure 6. Diagnostic approach to patients with a humeroperoneal pattern of weakness and suspected muscular dystrophy (Emery-Dreifuss muscular dystrophy)

*Autosomal dominant, autosomal recessive, or X-linked inheritance may be responsible in sporadic cases.

EDMD = Emery-Dreifuss muscular dystrophy.

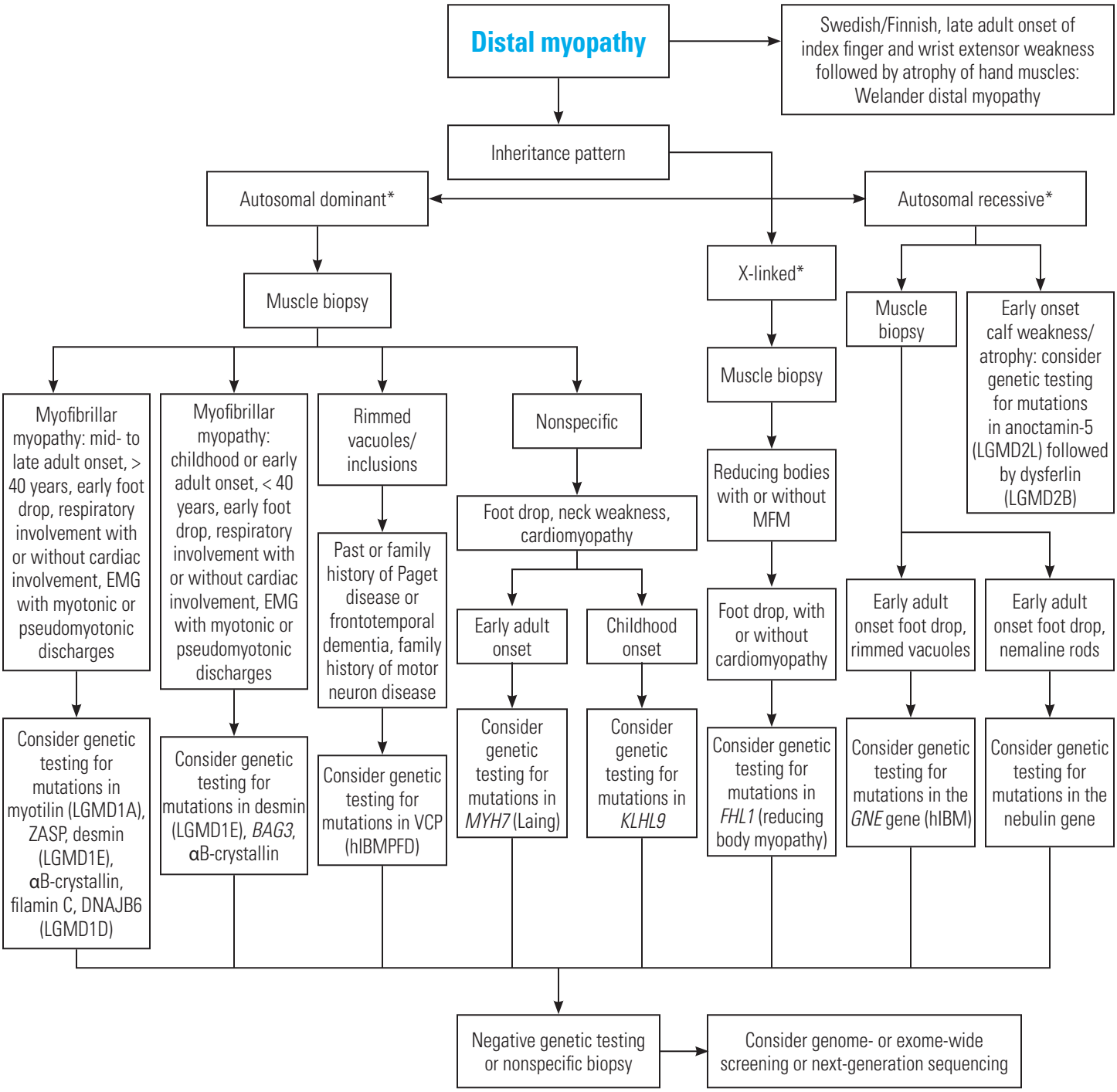

Figure 7. Diagnostic approach to patients with a distal pattern of weakness and suspected muscular dystrophy

*Autosomal dominant, autosomal recessive, or X-linked inheritance may be responsible in sporadic cases.

hIBM = hereditary inclusion body myopathy; hIBMPFD = hereditary inclusion body myopathy with Paget disease and frontotemporal dementia; LGMD = limb-girdle muscular dystrophy; MFM = myofibrillar myopathy; VCP = valosin-containing protein.

1. Bridges CB, Woods L, Coyne-Beasley T; Centers for Disease Control and Prevention ACIP Adult Immunization Work Group. Advisory Committee on Immunization Practices (ACIP) recommended immunization schedule for adults aged 19 years and older—United States, 2013. MMWR Surveill Summ 2013;62(Suppl 1):9–19.

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Definition of Clinical Context Terms
EVID = evidence-based conclusions for the systematic review
PRIN = (stipulated axiomatic) principles of care
RELA = (strong evidence from) related conditions not systematically reviewed

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