REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

The Dystrophinopathies

By Bo Hoon Lee, MD

ABSTRACT

PURPOSE OF REVIEW: This article reviews the history, epidemiology, genetics, clinical presentation, multidisciplinary management, and established and emerging therapies for the dystrophinopathies.

RECENT FINDINGS: The multidisciplinary care of individuals with dystrophinopathies continues to improve in many ways, including early surveillance and implementation of respiratory, cardiac, and orthopedic health management. The era of genetic therapeutics has altered the treatment landscape in neuromuscular disorders, including the dystrophinopathies.

SUMMARY: The dystrophinopathies are a spectrum of X-linked genetic disorders characterized by childhood-onset progressive weakness and variable cardiac and cognitive involvement. Corticosteroids are the mainstay of therapy to slow disease progression. Additional strategies for disease amelioration and dystrophin restoration, including gene replacement therapy, are under investigation.

CITE AS:
CONTINUUM (MINNEAP MINN) 2022;28(6, MUSCLE AND NEUROMUSCULAR JUNCTION DISORDERS):1678–1697.

Address correspondence to Dr Bo Hoon Lee, 601 Elmwood Ave, Box 631, Rochester, NY 14642, Bohoon_lee@urmc.rochester.edu.

RELATIONSHIP DISCLOSURE:
Dr Lee has received personal compensation in the range of $500 to $4,999 for serving on a scientific advisory or data safety monitoring board for AMO Pharma and F. Hoffmann-La Roche AG. The institution of Dr Lee has received research support from AMO Pharma, Novartis, Sanofi, and Sarepta Therapeutics.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Lee discusses the unlabeled/investigational use of allogenic cell therapy, ataluren, follistatin, gene therapy, pamrevlumab, and vamorolone for the treatment of Duchenne muscular dystrophy.

INTRODUCTION

The dystrophinopathies include a spectrum of neuromuscular disorders characterized by problematic function of the dystrophin protein, encoded by the *DMD* gene, located on the X chromosome. The dystrophinopathies are characterized by childhood-onset progressive muscle weakness but can have variable onset of symptoms and variable clinical progression.

HISTORY

The first historical report of Duchenne muscular dystrophy appeared in 1830 by Sir Charles Bell in an essay describing boys with progressive weakness.[1] The disorder was further characterized in the 1860s by Guillaume Duchenne, after whom the disorder is named. Sir William Richard Gowers documented the "peculiar way" in which several affected boys would rise from the floor in what is now referred to as the Gowers maneuver or Gowers sign.[2] Nearly a century later in 1955, Peter Emil Becker proposed a less severe form of the same disorder, now known as Becker muscular dystrophy, based on familial case series with similar clinical features.[3] In 1986 the genetic basis of the dystrophinopathies was elucidated, which was quickly followed by the identification of its protein product, dystrophin.[4–6] Corticosteroids entered widespread use in the early 2000s after demonstrating clear efficacy in muscle strength and functional outcomes.[7] Currently over 50 interventional studies are

registered on ClinicalTrials.gov recruiting participants with Duchenne muscular dystrophy.

EPIDEMIOLOGY

Duchenne muscular dystrophy is the most common form of muscular dystrophy with a worldwide incidence of approximately 1 in 3500 to 5000 live male births.[8] A milder form, Becker muscular dystrophy, is less common with an estimated incidence of 1 in 18,500 live male births.[9,10] Recent advances in genetic therapeutic strategies for Duchenne muscular dystrophy, which are discussed in more detail later in this article, have increased the interest in establishing Duchenne muscular dystrophy as a screened disorder through newborn screening panels, which may further inform the incidence and prevalence of the dystrophinopathies in various populations.[11]

GENETICS

It is important to understand the molecular genetics of the dystrophinopathies, their inheritance patterns, and the implications of this information for patients and their families.

DMD Gene and Inheritance

The *DMD* gene is th'e largest gene in the human genome, occupying approximately 2.5 million base pairs and consisting of 79 exons. It is located on the short arm of the X chromosome (Xp21.3-p21.2), accounting for about 1% of the chromosome.[4,5] Due to the location on the X chromosome, the dystrophinopathies are inherited in an X-linked manner such that hemizygous males are affected, heterozygous females may be unaffected or mildly affected, and sibling risk depends on the genetics of the mother. The *DMD* gene has a relatively high rate of spontaneous variation and approximately one-third of *DMD* mutations occur de novo.[12] Most patients with Duchenne muscular dystrophy have either an exon-level deletion (68% to 72%) or duplication (8% to 11%) concentrated in two mutational hot spots.[13,14] About 20% have smaller deletions/duplications or point mutations.[13,14] Confirming a molecular diagnosis is important for informing predicted phenotype and eligibility for genetic treatment modalities.

DMD Carriers

Females with classic Duchenne muscular dystrophy are rare but can be explained by several genetic mechanisms, including monosomy X (45 X; Turner syndrome), skewed X inactivation of the normal X chromosome, uniparental disomy, and compound heterozygosity or biallelic pathogenic variants. Most female carriers are asymptomatic. Symptomatic carriers typically manifest with mild muscle weakness and myalgia.[15] Carrier females have an increased risk of cardiac involvement whether or not skeletal muscle symptoms are present.[16] The most common findings include subclinical left ventricular dilation and dilated cardiomyopathy, but severe cardiac symptoms have been reported.[17–19] All carrier females are recommended to undergo a baseline cardiac evaluation in early adulthood followed by ongoing surveillance, but the optimal frequency of evaluations is not yet delineated.[20] Carrier testing and genetic counseling are recommended for all mothers of boys with confirmed Duchenne muscular dystrophy for the cardiac surveillance implications, to inform familial risk, and for reproductive planning (CASE 6-1).

KEY POINTS

- Duchenne muscular dystrophy is the most common muscular dystrophy, affecting 1 in 3500 to 5000 males.
- *DMD* is the largest gene in the human genome and has a high rate of spontaneous variation.
- The dystrophinopathies are X-linked genetic disorders due to pathogenic variation in the *DMD* gene. Approximately one-third of *DMD* mutations occur de novo.
- Females with heterozygous *DMD* mutations are often asymptomatic but can manifest mild skeletal muscle symptoms and/or cardiac involvement. Identified carriers should be referred to a cardiologist for surveillance.

Reading-Frame Rule

The reading-frame rule maintains that genomic variants that preserve the open reading frame (ie, in-frame variants) in the spliced mRNA give rise to milder phenotypes, whereas genomic variants that disrupt the open reading frame (ie, out-of-frame variants) result in more severe phenotypes. FIGURE 6-1 is a depiction of how these different variations affect the dystrophin construct based on the reading-frame rule. Many genetic testing laboratories will report whether a pathogenic variant in the *DMD* gene is known or predicted to disrupt or preserve the reading frame. Additionally, several databases (listed under "Useful Websites" at the end of the article) are available where this information can be queried. Exceptions to the reading-frame rule do occur in

CASE 6-1

A 4-year-old boy presented to a child neurology clinic for evaluation of delayed motor milestones. He had just started preschool and his teachers noted that he fell more frequently than his peers. He was born full term following an uncomplicated pregnancy and delivery. Developmentally, his parents reported that he was sitting independently at 9 months, pulling up to stand at 15 months, cruising by 18 months, and walking unsupported at 24 months. He sometimes walked on his toes but could walk flat-footed when reminded. His parents described him as a clumsy, happy child. He had no language delays and spoke in full sentences. He had an older sister without any developmental delays and a 20-month-old brother who had not yet started walking independently. His parents reported no history of known medical problems for themselves.

On examination, the patient was alert and interactive. He had normal tone throughout, with the exception of mildly increased tone at his bilateral ankles with restriction of dorsiflexion. When rising from the floor, he was noted to use his upper extremities and push off his thighs. His calves were enlarged. His reflexes were 1+ and symmetric. He was unable to hop and had minimal floor clearance when asked to jump. He was noted to have an exaggerated lumbar lordosis and hip sway with running.

A diagnosis of Duchenne muscular dystrophy was suspected. Laboratory investigation revealed creatine kinase of 10,802 U/L, aspartate transaminase of 333 U/L, and alanine transaminase of 550 U/L. Genetic testing revealed a deletion of exon 51 in the *DMD* gene. His mother was found to be a carrier of the deletion. His brother was evaluated because of the family history and motor delay and was also found to have the same pathogenic *DMD* deletion. His mother was referred to cardiology and the patient and his brother both established care in the pediatric neuromuscular clinic. The patient's parents were counseled that his sister has an approximately 50% risk of being a carrier.

COMMENT

This case demonstrates the classic presentation of a boy with Duchenne muscular dystrophy. The implications for familial risk counseling and testing are also illustrated.

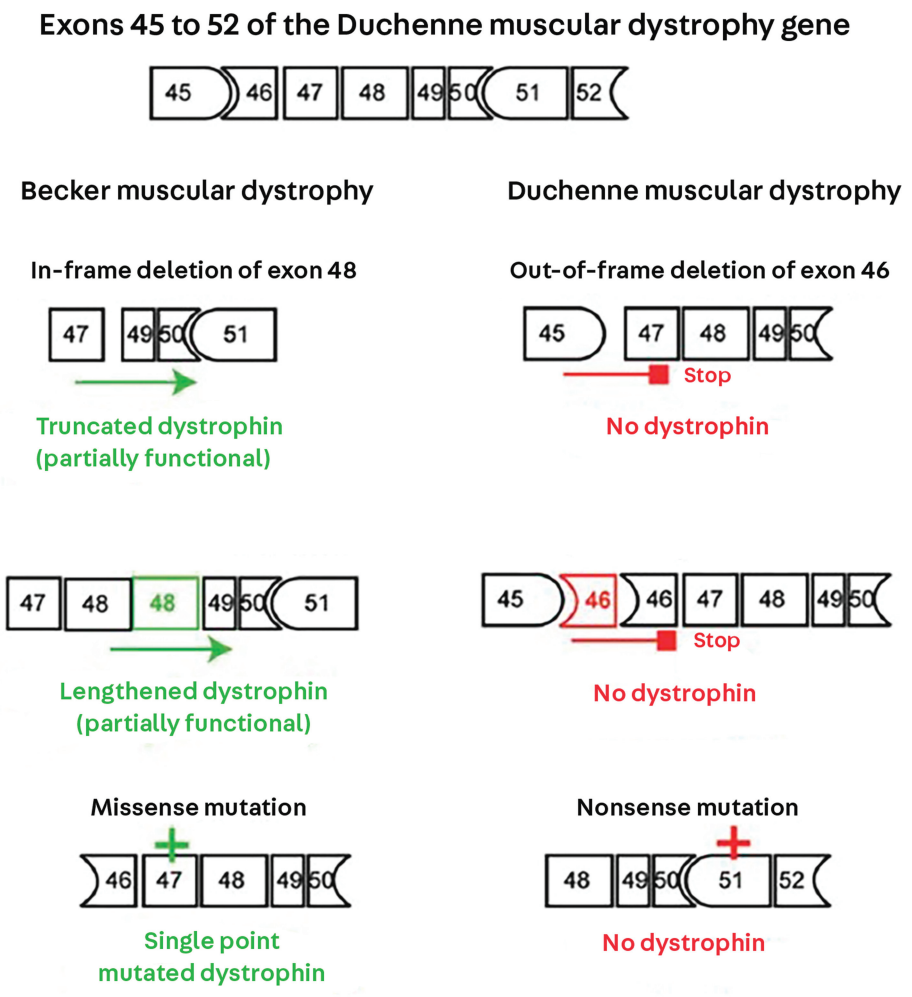

FIGURE 6-1

Schematic representation of dystrophin constructs based on genetic variation and the corresponding phenotype (Becker muscular dystrophy versus Duchenne muscular dystrophy). Exons are represented as boxes. Flat faces indicate that the exon codes for an entire protein sequence based on three-base codons (eg, exons 47, 48, and 49). Curved faces indicate that the exon does not code for an entire protein sequence, but that either the first or the last bases need the preceding or following exon to code a full three-base codon (eg, exons 50, 51, and 52).

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about 10% of patients with Duchenne muscular dystrophy/Becker muscular dystrophy.[13] Well-known exceptions include frameshift or nonsense variants before exon 8 due to the presence of alternative translation initiation sites, variants flanking exon 44 due to low-level spontaneous skipping of exon 44, and in-frame mutations in certain locations that significantly alter interactive or binding domains rendering a nonfunctional protein.[12] It is important to remember that phenotype predictions based on genotype alone are not always accurate. Clinical variability of skeletal and cardiac disease progression is seen in recurrently found mutations, even among individuals of the same family with the same genetic variant. Environmental, socioeconomic, and additional genetic modifiers likely contribute to this variability. Genetic modifiers are separate genetic loci that alter

KEY POINTS

- The genotype-phenotype relationship in Duchenne and Becker muscular dystrophies often follows the reading-frame rule whereby in-frame mutations predict milder Becker muscular dystrophy phenotype and out-of-frame mutations predict Duchenne muscular dystrophy phenotype.
- Exceptions to the reading-frame rule occur in about 10% of patients and variability is seen even among individuals with the same *DMD* genotype. Environmental, socioeconomic, and additional genetic modifiers likely contribute to this variability.

KEY POINTS

- Dystrophin is part of a membrane-stabilizing complex and protects the muscle from injury during contraction. Absence of dystrophin therefore leads to destabilization and cellular damage.
- A dystrophinopathy should be suspected in any young boy presenting with gross motor delay. Cognitive, behavioral, and speech/language delays can be early presenting symptoms.

the phenotype of a genetic disorder. *SPP1*, *CD40*, and *LTBP4* are among the genes recently recognized as genetic modifiers of the dystrophinopathies.[21,22]

Dystrophin and the Dystrophin-Associated Protein Complex

DMD gene expression gives rise to seven distinct tissue-specific isoforms of dystrophin generated through alternative splicing events.[23] Full-length dystrophin is predominantly expressed in skeletal and cardiac muscle and, to a lesser degree, cortical neurons.[23] Dystrophin is located on the cytoplasmic side of the plasma membrane and has four functional domains: the amino terminal actin-binding domain, the rod domain, the cysteine-rich domain, and the carboxy-terminal domain. Dystrophin is part of a large glycoprotein complex known as the dystrophin-associated protein (DAP) complex (FIGURE 6-2[24]). The DAP complex connects the intracellular actin to the basal lamina through the extracellular matrix, thereby stabilizing the membrane during muscle contraction. Pathogenic variants in genes encoding other proteins involved in the DAP complex result in a variety of muscular dystrophies, as depicted in FIGURE 6-2. Loss or absence of dystrophin leads to destabilization of the sarcolemma, increased membrane permeability, and subsequent cellular damage and muscle degeneration followed by fibrosis and fatty replacement.

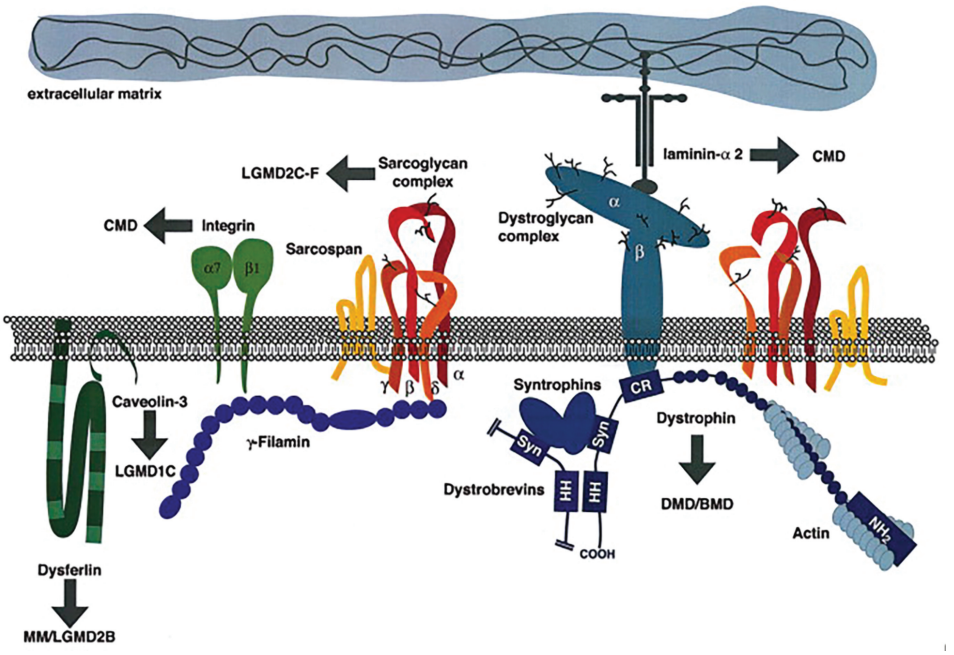

FIGURE 6-2

Dystrophin associated protein complex. Arrows indicate the proteins involved in other muscular dystrophies. Dystrophin is involved in the mechanical stabilization of the sarcolemma. Mutations in the sarcoglycan proteins, caveolin-3, and dysferlin lead to forms of limb-girdle muscular dystrophy (LGMD). Laminin α-2 chain is mutated in a subtype of congenital muscular dystrophy (CMD) without structural brain anomalies, as is α7-integrin.

COOH = carboxy-terminal domain; CR = cysteine-rich domain; DMD/BMD = Duchenne muscular dystrophy/Becker muscular dystrophy; HH = two helices of the coiled-coil domain; MM = Miyoshi myopathy; NH_2 = amino-terminal domain; Syn = syntrophin-binding domain.

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CLINICAL PRESENTATION

The dystrophinopathies are a spectrum disorder with wide variability in clinical onset and progression but classically have been classified by severity into Duchenne and Becker muscular dystrophies. An intermediate type and a Duchenne muscular dystrophy–associated cardiomyopathy phenotype also exist.

Duchenne Muscular Dystrophy

Duchenne muscular dystrophy most commonly presents with gross motor delay. Clinical symptoms are typically absent at birth and during infancy, although a mild delay in gross motor milestone achievement may be present, particularly in independent ambulation. The most common early signs and symptoms include gross motor delay, delayed ambulation or abnormal gait, persistent toe-walking, and, less commonly, speech or cognitive delays.[25] Duchenne muscular dystrophy may sometimes be identified during clinical evaluation for unexplained laboratory abnormalities including transaminitis and elevated lactate dehydrogenase. Functionally, parents will often describe children as being clumsy and note that they fall more frequently than their peers or have a hard time keeping up. Parents may also report that the child has difficulty with running, climbing, or standing up from the floor. On examination, a typical pattern of weakness may be seen involving proximal lower limb muscles first resulting in clinical cues like the Gowers sign, which is when a child with a weak pelvic girdle uses their hands as a compensatory measure to climb up their legs to get from supine to standing. Additional findings on examination typically include a wide-based "waddling" gait with an exaggerated lumbar lordosis and bilateral calf enlargement. The gradual enlargement of the gastrocnemii muscles in Duchenne muscular dystrophy is usually a phenomenon of true hypertrophy initially as excessive compensatory use of distal muscles occurs, but later in the disease course, it reflects the replacement of muscle by fat and connective tissue. This phenomenon, known as *pseudohypertrophy*, is seen in FIGURE 6-3. Ankle

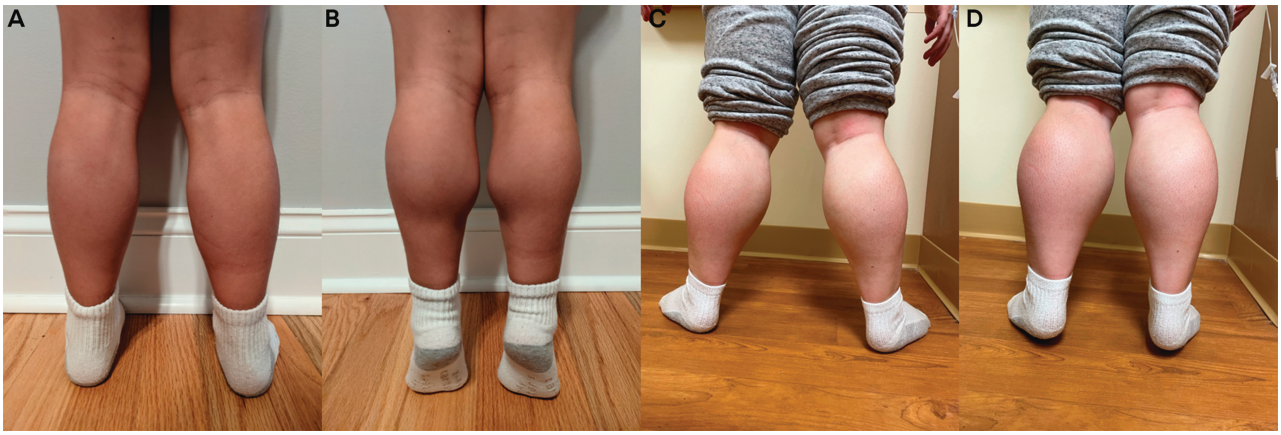


FIGURE 6-3

Enlargement of gastrocnemii muscles in a 4-year-old boy with Duchenne muscular dystrophy standing plantigrade (*A*) and on tiptoes (*B*) and in a 13-year-old boy with Duchenne muscular dystrophy (*C, D*). Note the progressive hypertrophy and widened based in the older boy (*C*) and equinus contracture appreciated when asked to narrow his base (*D*).

plantar flexors often remain relatively strong early in the disease course. Cranial nerve innervated muscles, with the exception of the sternocleidomastoids, are selectively spared in the dystrophinopathies. CASE 6-1 describes the typical presentation of Duchenne muscular dystrophy.

The predictable sequence of progression is often categorized into four clinically descriptive phases: early ambulatory, late ambulatory, early nonambulatory, and late nonambulatory.[26] During the early ambulatory phase, children typically attain additional motor skills prior to plateauing and clinical decline. Treatment with glucocorticoids is usually started during the early to late ambulatory stages. The transition between the late ambulatory and early nonambulatory stage is a sentinel event marker of Duchenne muscular dystrophy progression. Wheelchair dependency traditionally occurs before age 13 in Duchenne muscular dystrophy. The development of joint contractures occurs as muscle weakness progresses. The loss of ambulation is often followed by the need for initiation or escalation of respiratory interventions and signs or symptoms of cardiac dysfunction. Morbidity and mortality in Duchenne muscular dystrophy are predominantly caused by cardiopulmonary complications. Life expectancy trends have consistently shown improved survival, with recent studies showing a median survival of 28.1 years in individuals with Duchenne muscular dystrophy born after 1990.[27]

Becker Muscular Dystrophy

Becker muscular dystrophy is the milder spectrum of the dystrophinopathies. Historically, age at loss of ambulation has been used to clinically distinguish between Becker muscular dystrophy and Duchenne muscular dystrophy. Boys with Becker muscular dystrophy lose ambulation after age 15. The spectrum of symptom variability is wider in Becker muscular dystrophy. The average age of symptom onset is typically between early childhood and young adulthood but occasionally occurs beyond the fourth decade.[28,29] Cardiac involvement can be prominent in Becker muscular dystrophy and does not necessarily correlate with skeletal muscle involvement. Some researchers suggest that the ability to perform strenuous exercise in mild Becker muscular dystrophy leads to high-pressure mechanical stress on the vulnerable dystrophin-deficient myocardial cells and worsening cardiomyopathy.[30] It is worth mentioning a distinct primary cardiac phenotype in some individuals with a *DMD* mutation, X-linked dilated cardiomyopathy, that presents with congestive heart failure in teenage males with little to no skeletal muscle involvement.

Intermediate Duchenne Muscular Dystrophy

A small group of individuals presents with "mild Duchenne muscular dystrophy" or "severe Becker muscular dystrophy" that are recognized as intermediate *DMD* phenotypes. This includes the group of individuals who lose ambulation after age 12 to 13 but before age 16.

DIAGNOSIS

In the absence of family history, diagnostic delay by approximately 2.5 years after symptom onset is common in Duchenne muscular dystrophy despite the increasing availability of molecular diagnostic testing capabilities and disease-modifying treatments.[25,31]

Differential Diagnosis

Several limb-girdle muscular dystrophies (LGMDs) can resemble Duchenne muscular dystrophy/Becker muscular dystrophy. These include sarcoglycanopathies (LGMD types 2C to 2F), a group of disorders resulting from genetic defects in one of the four sarcoglycan transmembrane proteins that are part of the DAP complex (FIGURE 6-1).[32] Fukutin-related proteinopathy (LGMD 2I) can present as a Duchenne muscular dystrophy–like phenotype, especially with the occurrence of dilated cardiomyopathy and respiratory involvement.[33] The LGMDs are predominantly inherited in an autosomal dominant or recessive manner, so a careful pedigree can sometimes illuminate the most likely inheritance pattern. Calf pseudohypertrophy tends to be less prominent in the LGMDs compared to Duchenne muscular dystrophy/Becker muscular dystrophy. Other neuromuscular disorders presenting in childhood with a limb-girdle pattern of weakness include spinal muscular atrophy, Pompe disease, Emery-Dreifuss muscular dystrophy, and other congenital muscular dystrophies. These can often easily be distinguished from Duchenne muscular dystrophy/Becker muscular dystrophy with a few additional investigations.

Laboratory Investigation

If a family history of Duchenne muscular dystrophy/Becker muscular dystrophy is present, any sign or symptom should prompt laboratory screening with a creatine kinase (CK) level. If no family history of Duchenne muscular dystrophy/Becker muscular dystrophy is present, a boy presenting with any of the aforementioned symptoms (eg, gross motor delay, toe walking, Gowers sign) should prompt this investigation (FIGURE 6-4). CK screening should also be considered in patients with unexplained transaminitis or elevations in lactate dehydrogenase. CK is invariably elevated to 5 to 10 times the upper limits of normal in Duchenne and Becker muscular dystrophies. A normal CK essentially rules out a diagnosis of Duchenne muscular dystrophy/Becker muscular dystrophy. This CK elevation is present presymptomatically and at birth, allowing it to be a potential first-tier marker on newborn screening panels.[11]

Molecular Genetic Testing

Appropriate genetic testing should be performed to confirm clinical suspicion of a dystrophinopathy. A specific genetic diagnosis is critical given the implications for eligibility for clinical trials and genetic-based treatments. Genetic testing can be done either in a stepwise fashion or in parallel for *DMD* deletion/duplication testing via multiplex ligation-dependent probe amplification (MLPA) and next-generation sequencing. A recent study using genome and muscle RNA sequencing found splice-altering intronic variants or structural rearrangement in seven males with high clinical suspicion for dystrophinopathy and negative MLPA and sequencing results.[34]

Muscle Biopsy

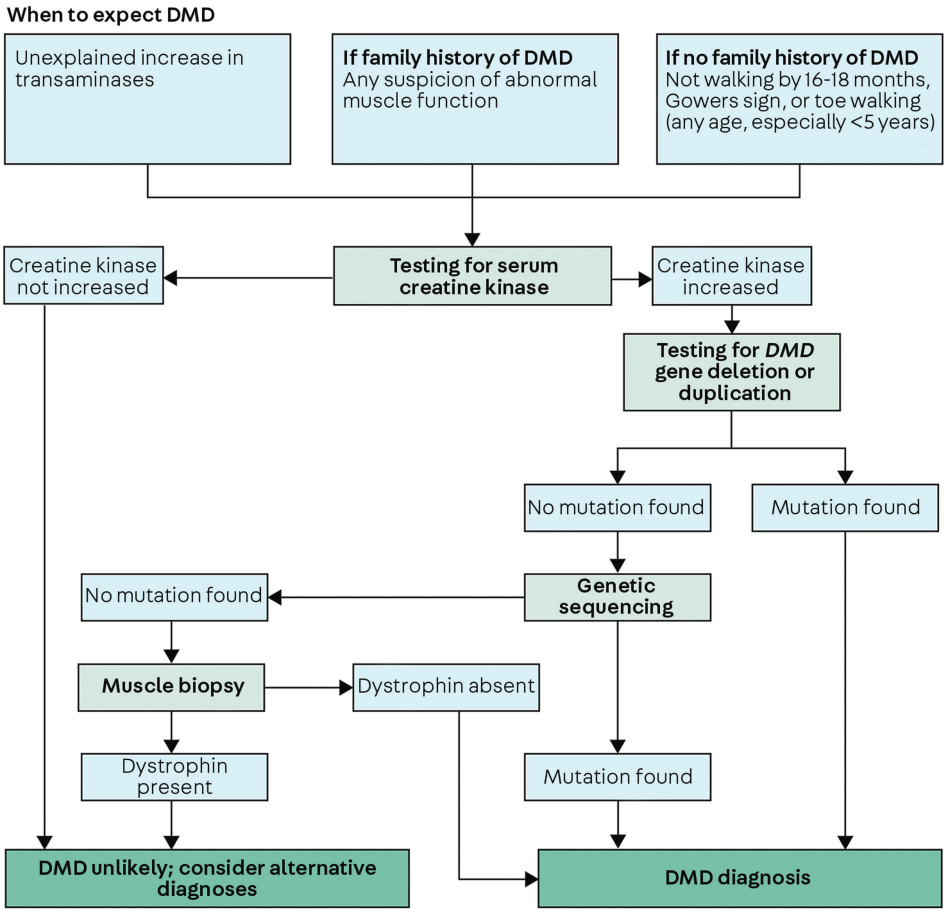
Although the use of routine skeletal muscle biopsy is less common due to the increasing availability of rapid genetic testing, it remains useful in some clinical cases and certainly as a measure of dystrophin restoration with treatment in clinical trial and research settings. Muscle biopsy can be helpful when the clinical presentation is incongruent with the predicted phenotype (eg, individuals with

KEY POINTS

- The predictable progression in Duchenne muscular dystrophy is often categorized into the following phases: early ambulatory, late ambulatory, early nonambulatory, and late nonambulatory.
- Loss of ambulation with wheelchair dependency is a sentinel marker of progression and typically occurs by age 13 years in Duchenne muscular dystrophy and after age 16 years in Becker muscular dystrophy.
- Duchenne and Becker muscular dystrophies are the most common muscular dystrophies. As care across the spectrum improves, individuals with Duchenne muscular dystrophy and Becker muscular dystrophy are surviving longer into adulthood and requiring transitions of care from pediatric to adult specialists.
- Becker muscular dystrophy is milder than Duchenne muscular dystrophy and can have much more variability in symptom onset and progression, but symptom onset in childhood and early adulthood is typical.
- Several limb-girdle muscular dystrophies can resemble the dystrophinopathies but can be distinguished by clinical features, familial inheritance pattern, and additional testing.

KEY POINTS

- **Serum creatine kinase is the best initial diagnostic test when suspecting a dystrophinopathy. Creatine kinase is 5 to 10 times the upper limits of normal in Duchenne and Becker muscular dystrophies.**
- **Genetic testing should be performed to confirm a suspected diagnosis of Duchenne or Becker muscular dystrophy. Rarely, when genetic testing is negative, muscle biopsy may be necessary.**
- **The histopathologic features of muscle in the dystrophinopathies include evidence of active and chronic myopathy, increased endomysial connective tissue fibrosis, and fat accumulation. Immunohistochemical staining for dystrophin will demonstrate reduced or absent staining.**



Most commonly observed signs and symptoms in patients with DMD

Motor	Nonmotor
Abnormal gait	Behavioral issues
Calf pseudohypertrophy	Cognitive delay
Inability to jump	Failure to thrive or poor weight gain
Decreased endurance	Learning and attention issues
Decreased head control when pulled to sit	Speech delay or articulation difficulties
Difficulty climbing stairs	
Flat feet	
Frequent falling or clumsiness	
Gowers sign on rising from the floor	
Gross motor delay	
Hypotonia	
Inability to keep up with peers	
Loss of motor skills	
Muscle pain or cramping	
Toe walking	
Difficulty running or climbing	

FIGURE 6-4

An algorithm for diagnosis of Duchenne muscular dystrophy (DMD).

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in-frame mutations presenting with a Duchenne muscular dystrophy phenotype) or when there is a question of a manifesting carrier. Additionally, in rare situations where genetic testing is negative, muscle immunohistochemical analysis can be informative. Open muscle biopsies should ideally be done by an experienced surgeon and handled by an experienced laboratory for handling and preparation.

The pathologic features of dystrophic muscle are the combination of degeneration with active and chronic regeneration. Histopathologic features on muscle biopsy include evidence of active and chronic myopathy, increased endomysial connective tissue fibrosis, and fat accumulation (FIGURE 6-5). Additionally, large hypercontracted fibers can be seen, reflective of fiber fragility due to the lack of supporting scaffold of the dystrophin protein. Muscle biopsy for Duchenne muscular dystrophy should include immunohistochemistry for dystrophin and ideally should be interpreted by an experienced neuromuscular pathologist (FIGURE 6-6). Immunohistochemical panels often include additional antibodies for the nondystrophin targets spectrin and utrophin. Spectrin staining should be retained regardless of dystrophin expression, whereas sarcolemmal expression of utrophin is often dramatically increased in dystrophin-deficient muscle.

While the role of skeletal muscle biopsy in the clinical diagnosis of dystrophinopathies has been diminishing, it remains a useful tool as an outcome measure for therapeutic response in the era of genetic therapeutics including exon skipping and microdystrophin gene delivery.

Muscle Ultrasound

Skeletal muscle ultrasound is a noninvasive imaging tool for measuring muscle pathology and is becoming increasingly popular. This modality is a relatively quick, painless bedside procedure that can be followed serially and has been shown to be feasible for use in all ages including the very young.[35] Increases in fatty replacement and muscle fibrosis are reflected in changes to the muscle echo

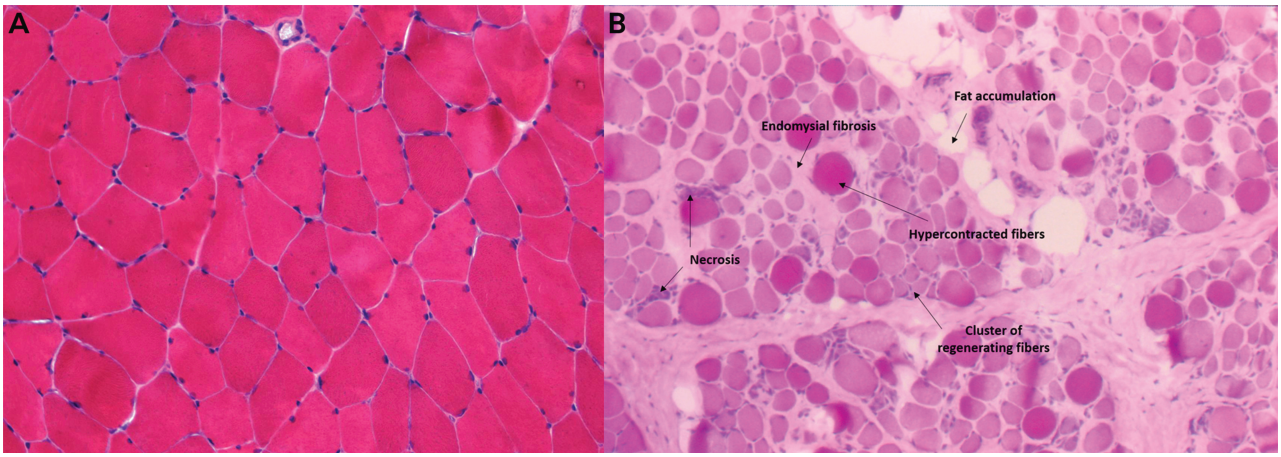

FIGURE 6-5

Hematoxylin and eosin (H&E) stained biopsy slides of normal muscle (*A*) and from a patient with Duchenne muscular dystrophy (*B*) demonstrating muscle atrophy, necrosis, regeneration, and endomysial fibrosis and fat accumulation.

Figure courtesy of Rabi Tawil MD.

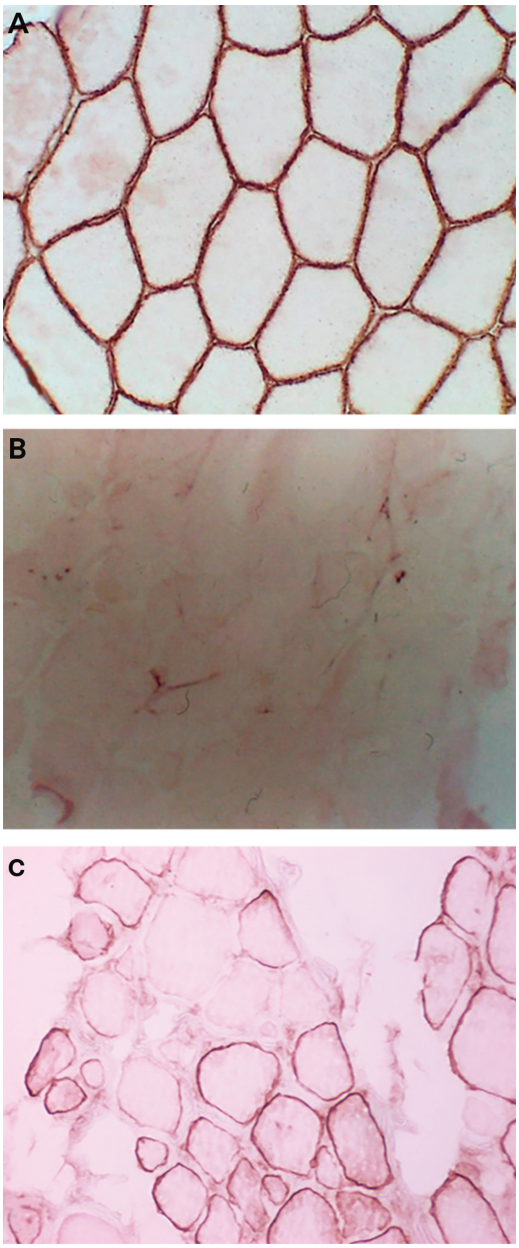

FIGURE 6-6

Immunostaining for dystrophin from muscle biopsy samples showing (*A*) complete and normal staining of dystrophin in a healthy individual, (*B*) absent staining in a patient with Duchenne muscular dystrophy, and (*C*) some normally staining fibers and some fibers with little to no dystrophin staining in a manifesting carrier.

Figure courtesy of Rabi Tawil, MD.

intensity on ultrasound. These changes have been shown to correlate with worsening strength and function over time.[36] Interestingly, these progressive ultrasound changes have also been seen in young boys despite improving clinical function.[35]

Muscle MRI

A distinctive MRI pattern of muscle involvement has been characterized in Duchenne muscular dystrophy which includes early edema and inflammation followed by intramuscular fatty infiltration.[37] Quantitative MR imaging is increasingly recognized as a high-quality biomarker capable of predicting functional decline and loss of ambulation.[38] Noninvasive muscle imaging is an additional tool for monitoring disease progression that is not as dependent on patient participation, and will likely play an important role in measuring the clinical efficacy of new therapeutic options. Acquisition time and claustrophobia could be logistical barriers for routine clinical use of muscle MRI.

Other Tests

EMG is rarely necessary in the diagnosis of dystrophinopathies.

MANAGEMENT

The clinical management of the dystrophinopathies is multidisciplinary and ideally involves an integrated team approach involving the following specialties: neuromuscular neurology, cardiology, developmental and behavioral pediatrics, endocrinology, gastroenterology, genetics, nutrition, orthopedics, physical therapy, pulmonology, and psychology. The detailed management of multisystem involvement is not within the scope of this article, but a few important factors are highlighted here.

Cardiac

The cardiac manifestations of dystrophinopathy are a leading cause of morbidity and mortality in patients with dystrophinopathies. Cardiomyopathy-related mortality from Duchenne muscular dystrophy is higher than that for other dilated cardiomyopathies, but it is often underrecognized and undertreated.[39,40] Cardiac dysfunction can manifest as nonspecific abnormalities on ECG and evolves toward dilated cardiomyopathy reflective of widespread endocardial fibrosis. The early detection and treatment of cardiac dysfunction are important. Routine annual cardiac surveillance should begin in childhood at diagnosis or by 6 to 7 years old with ECG and noninvasive imaging. The imaging modality of choice is cardiac MRI, particularly in nonambulatory boys given the technical limitations of echocardiograms due to coincident chest wall deformities and scoliosis and pulmonary disease at this stage. The use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers should begin by age 10, and earlier initiation should be considered.[41,42]

Respiratory

Respiratory manifestations are another major cause of morbidity and mortality in Duchenne muscular dystrophy. Over the past several decades, improvements in respiratory care have increased the life expectancy of patients with Duchenne muscular dystrophy from young adulthood into the fourth decade.[41] Respiratory progression occurs from a combination of progressive diaphragmatic weakness, worsening chest wall compliance, and ineffective clearance. Respiratory management includes anticipatory monitoring for signs and symptoms of respiratory decline and timely implementation of lung volume recruitment techniques, cough assist, and ultimately noninvasive and invasive ventilatory support. Lung function tests should begin at age 5 to 6 years and be monitored serially thereafter. Decline in forced vital capacity (FVC) correlates with muscular weakness and progression to respiratory failure.[41] The risk of respiratory compromise increases significantly after the loss of ambulation. Spirometry should be done at least twice yearly in patients who are nonambulatory or once FVC falls below 80%. Sleep-disordered breathing and nocturnal hypoventilation can be an early manifestation of respiratory involvement. Nocturnal noninvasive ventilatory support should be initiated in boys when FVC falls below 50% predicted and/or evidence is present of sleep-disordered breathing or obstructive sleep apnea. Daytime assisted ventilation should be added if clinical symptoms of dyspnea are present, or when daytime oxygen saturation is below 95% and/or blood $PaCO_2$ is greater than 45 mm Hg. This can be extended up to 24 hours a day and is often preferred over tracheostomy, which may be indicated in certain individuals.[43] Proactive optimization of pulmonary regimen with lung volume recruitment strategies, cough assist, and assisted ventilation should be done perioperatively or postoperatively and during respiratory illness. Inactivated influenza and pneumococcal vaccines should be recommended annually.

Musculoskeletal

Due to the combination of progressive muscle weakness, increasing immobility, and chronic glucocorticoid exposure, boys with Duchenne muscular dystrophy and Becker muscular dystrophy encounter several orthopedic and musculoskeletal complications. They are at high risk for low-trauma bone

KEY POINTS

- Muscle imaging via ultrasound and MRI are increasingly being used as additional measures of disease progression.
- The dystrophinopathies are multisystem disorders and best served by a multidisciplinary care approach that includes neurology, cardiology, developmental and behavioral pediatrics, endocrinology, gastroenterology, genetics, nutrition, orthopedics, physical therapy, pulmonology, and psychology.
- Cardiac surveillance in patients with dystrophinopathies should start at diagnosis or early childhood. Initiation of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers is recommended by age 10 for boys with Duchenne muscular dystrophy.
- Surveillance for respiratory involvement in patients with dystrophinopathies is recommended along with evaluation for sleep-disordered breathing and nocturnal hypoventilation. Patients benefit from timely implementation of lung volume recruitment techniques, cough assist, and ultimately noninvasive and invasive ventilatory support.

fractures and vertebral fractures. Surveillance with regular spine imaging is recommended. Identification of either symptomatic or asymptomatic vertebral fractures should prompt referral to an osteoporosis expert for consideration of IV bisphosphonates.[41] Contracture and scoliosis surveillance and management are also core orthopedic needs in patients with Duchenne/Becker muscular dystrophy. Correction of scoliosis has been shown to have an additive effect on survival when combined with nocturnal ventilation.[44]

Physical Therapy

Serial assessments of muscle strength and function should be performed to help guide steroid management and physical therapy interventions. Commonly used tests are summarized in TABLE 6-1. Timed function tests like the 6-minute walk test and time to rise are clinically meaningful ways to monitor disease progression but are limited to use in ambulatory patients. The North Star Ambulatory Assessment is a widely used 17-item rating scale specifically developed for boys with Duchenne muscular dystrophy. Timed function tests and the North Star Ambulatory Assessment have been shown to reliably and reproducibly predict decline in motor function and ambulation.[45]

Neurocognitive and Neurobehavioral

The cognitive and behavioral phenotype of the dystrophinopathies has long been recognized and can sometimes be what brings patients to the attention of a specialist, as illustrated in CASE 6-2. A higher prevalence of varying degrees of intellectual disability, autism spectrum disorder, attention deficit hyperactivity

TABLE 6-1 **Commonly Used Outcome Measures and Motor Assessments in Duchenne and Becker Muscular Dystrophies**

Muscle strength	Manual muscle testing
	Quantitative myometry
Muscle function	North Star Ambulatory Assessment (NSAA)
	Brooke upper extremity scale
	Hammersmith functional motor scale (HMFS)
	Performance of the Upper Limb (PUL)
	Motor Function Measure
	Bayley-III Scales of Infant and Toddler Development[a]
Timed test	6-minute walk test
	Time to rise (supine to stand)
	10-meter run
	Four-stair climb
	Four-stair descend

[a] Bayley-III assesses cognitive and language components in addition to motor scores.

disorder, obsessive-compulsive disorder, and other emotional and behavioral disturbances exists in boys with dystrophinopathies.[46] Multiple studies have found a correlation between mutation location near the 3' end of the *DMD* gene with increased incidence of neurodevelopmental symptoms, underscoring the likely importance of certain dystrophin isoforms.[46] Comprehensive care for patients with dystrophinopathies should include neuropsychiatric and neurodevelopmental evaluation and routine mental health screening.

TREATMENT

Recent therapeutic advancements in neuromuscular disorders are rapidly changing the treatment landscape of the dystrophinopathies. The two main intervention strategies are targeted at ameliorating disease pathology (eg, inflammation, fibrosis) and the restoration of dystrophin. An overview of the current landscape of disease-modifying therapy is summarized in TABLE 6-2.

Corticosteroids

Corticosteroids entered widespread use about 30 years ago after demonstrating clear efficacy in improving strength and function in clinical trials.[47] Despite

CASE 6-2

A 2-year-old boy was referred to a pediatric neuromuscular clinic after recent genetic testing diagnosed him with a dystrophinopathy. He had presented to a pediatric geneticist for genetic evaluation of global developmental delay and autism. He was born at 39 weeks gestation following an unremarkable and routine pregnancy, weighed 3.7 kg (8 pounds, 3 ounces) at birth, and did not require any specialized neonatal care. His parents reported that they were first concerned when he was not yet sitting or consistently rolling at age 7 months. He finally achieved both milestones around age 9 months, and was able to pull himself to standing at 17 months and independently ambulate at 19 months. At age 2 years, he was noted to only use three specific words and exhibited limited social communication.

He was initially evaluated by a developmental and behavioral pediatrician and diagnosed with autism spectrum disorder. A chromosomal microarray was recommended by the pediatric geneticist and showed a 126 kb loss at Xp21.1. Creatine kinase was checked and found to be elevated at 9705 U/L. Confirmatory *DMD* deletion/duplication analysis revealed deletion of exons 45 to 47 in *DMD*, prompting referral to a neuromuscular specialist.

On examination he was noted to be nonverbal, and had poor eye contact and diminished deep tendon reflexes throughout. He was observed to pull to stand independently but had not yet achieved independent ambulation.

COMMENT

This case illustrates that a subset of patients with dystrophinopathy may present with cognitive, language, and behavioral symptoms in addition to or even prior to the onset of motor weakness.

the position of corticosteroids as the mainstay of treatment for the dystrophinopathies, the exact mechanism of action, the optimal age for treatment initiation, and optimal dosing regimens remain areas requiring further clarification. Results from the FOR DMD (Finding the Optimal Dose for Duchenne Muscular Dystrophy) trial, which was designed to compare three commonly used regimens, suggest that boys who received daily corticosteroid administration had better outcomes at 3 years, most significantly as measured by rise from the floor velocity, compared to those who received the intermittent dosing regimen (10 days on, 10 days off). Other intermittent dosing regimens were not included in this study.[48] Commonly used dosing regimens for oral prednisone include daily 0.75 mg/kg/d dosing and intermittent dosing regimens including 5 mg/kg/d two times per week on consecutive days or 10 days on, 10 days off. Once started, dose adjustments due to side effects are common. The long-term side effects of corticosteroids are well described and include growth restriction, weight gain, behavioral symptoms, osteoporosis, and cataracts.

Deflazacort, an oxazoline derivative of prednisolone, was approved by the US Food and Drug Administration (FDA) for Duchenne muscular dystrophy in 2017, although it had been in clinical use for several decades in other countries.[49] The recommended once-daily dose of deflazacort is 0.9 mg/kg/d. Deflazacort has demonstrated equal efficacy for motor outcomes with less weight gain at 12 months of treatment as compared to prednisone, but longer-term comparisons are not available.[49] A higher risk of cataract formation is present with deflazacort.[50]

Corticosteroid therapy should be started before motoric decline, typically between ages 3 to 5 in Duchenne muscular dystrophy, but the exact age has not been delineated. Early initiation of treatment with twice-weekly corticosteroids has been proposed in infant and toddler boys.[51]

Vamorolone is a first-in-class steroid analogue that acts as a nuclear factor kappa-B inhibitor and is currently being investigated for use in Duchenne muscular dystrophy.[52,53]

TABLE 6-2 **Therapeutic Landscape of Duchenne Muscular Dystrophy, Including Drugs Recently Approved by the US Food and Drug Administration and Drugs Currently in Development**

Treatment modality	Pharmacologic agent
Corticosteroids	Prednisone, deflazacort[a]
Nuclear factor-kappa B inhibitor	Vamorolone
Stop-codon readthrough	Ataluren
Exon skipping	Eteplirsen (exon 51 skip-amenable),[a] golodirsen (exon 53 skip-amenable),[a] viltolarsen (exon 53 skip-amenable),[a] casimersen (exon 45 skip-amenable)[a]
Gene replacement	Mini-dystrophin, microdystrophin
Antifibrotic	Pamrevlumab
Muscle regeneration promoters	Follistatin, allogeneic cell therapy

[a]Drugs with FDA approval for use in Duchenne muscular dystrophy.

Exon Skipping

The antisense-mediated exon-skipping approach is aimed at the restoration of the reading frame in patients with out-of-frame deletions or duplications. This mutation-specific strategy could theoretically be applicable to 83% of all pathogenic Duchenne muscular dystrophy variants but is currently clinically available for approximately 42% of variants, as shown in TABLE 6-3.[54] Eteplirsen is an antisense oligonucleotide that selectively binds exon 51 and excludes it from the mature mRNA transcript. It was the first of its mechanistic group to receive conditional FDA approval in 2017 after demonstrating stabilization in timed motor function (6-minute walk test) and lower incidence of loss of ambulation over 36 months in 12 boys compared to historical controls.[55] Long-term follow-up outcomes in the 2 boys who lost ambulation during the study demonstrated relative stability in nonambulatory measures of disease progression including upper limb function and measures of cardiac and pulmonary function.[56] The 96-week open-label study (PROMOVI) data suggest slowed decline in FVC and 6-minute walk test measures when compared to untreated natural history cohorts.[57] Other exon-skipping targeted drugs have been subsequently approved, including golodirsen (targeting exon 53), viltolarsen (targeting exon 53), and casimersen (targeting exon 45). It is worth noting that these trials included only boys with Duchenne muscular dystrophy who are ambulatory at treatment initiation. Additional long-term clinical and real-world data are needed.

Stop-Codon Readthrough

Ataluren is an oral small-molecule drug that promotes "readthrough" of nonsense mutations, thereby allowing protein translation.[58] The drug was granted conditional approval in Europe for ambulatory patients over age 2 years after showing benefit in this subgroup but has been denied FDA approval in the US as the study failed to demonstrate improvement in the primary endpoint (ie, slowed progression as measured by change in the 6-minute walk distance).[59] Studies further investigating the efficacy of ataluren are ongoing.

Gene Replacement

Gene replacement therapy has been successful in other genetic neuromuscular conditions such as spinal muscular atrophy.[60] The historic obstacle for molecular manipulation and packaging of the *DMD* gene has been its large size. Clinical

Proportion of *DMD* Pathogenic Variants Amenable to Currently Available Variant-Specific Modalities TABLE 6-3

Treatment strategy	Duchenne muscular dystrophy patients amenable (%)
Stop-codon readthrough	13
Exon 45 skipping	8
Exon 53 skipping	8
Exon 51 skipping	13
None	58

KEY POINTS

- **There is a robust drug development pipeline for Duchene muscular dystrophy. Therapeutic approaches include restoration of dystrophin through genetic mechanisms (exon skipping, stop-codon readthrough, gene replacement) and disease amelioration through reduction of inflammation, fibrosis, and muscle protection.**
- **Corticosteroids slow the progression of disease in Duchenne muscular dystrophy and should be initiated before there is motoric decline, but the optimal age has not been delineated.**

observations of very mild phenotypes, including the well-known case of a 61-year-old ambulatory patient who harbored a large deletion involving 46% of the coding region, led to the concept that delivery of a "mini" or "micro" gene construct could be sufficient.[61] This technology uses an engineered truncated dystrophin gene construct along with muscle-specific promotors delivered in adeno-associated virus vectors. Early clinical trials are demonstrating promising results.[62,63]

CONCLUSION

Dystrophinopathies are genetic multisystem disorders with predominant involvement of the skeletal muscle, cardiac muscle, and brain. They are progressive disorders with accumulating morbidity, particularly following the loss of ambulation due to progressive cardiopulmonary dysfunction, worsening immobility, and consequences of long-term corticosteroid exposure. The management of dystrophinopathies ideally involves a coordinated multidisciplinary approach that addresses both primary and secondary aspects of the disorder. While there is no cure for Duchenne and Becker muscular dystrophies, the therapeutic landscape is rapidly evolving in the era of genetically based interventions.

USEFUL WEBSITES

CLINICALTRIALS.GOV
Up-to-date resource regarding clinical trials in dystrophinopathies.
clinicaltrials.gov

CUREDUCHENNE
CureDuchenne is a nonprofit organization in pursuit of improving advocacy and medical and therapeutic care for the Duchenne muscular dystrophy community.
cureduchenne.org

MUSCULAR DYSTROPHY ASSOCIATION
The Muscular Dystrophy Association is a national nonprofit group connecting families affected by muscular dystrophies, providers, and investigators through care, advocacy, and research.
mda.org

PARENT PROJECT MUSCULAR DYSTROPHY
Parent Project Muscular Dystrophy is a national nonprofit organization focused on Duchenne muscular dystrophy advocacy and research.
parentprojectmd.org

UMD TREAT-NMD DMD MUTATIONS DATABASE
The UMD TREAT-NMD DMD database is a searchable, publicly available variant database.
umd.be/TREAT_DMD

LEIDEN MUSCULAR DYSTROPHY PAGES
The Leiden muscular dystrophy database is a searchable, publicly available variant database.
dmd.nl/index

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