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PRACTICE RESOURCE

Genetic counseling for the dystrophinopathies—Practice resource of the National Society of Genetic Counselors

Angela M. Pickart[1] | Ann S. Martin[2] | Brianna N. Gross[3] | Lisa M. Dellefave-Castillo[4] | Leslie M. McCallen[5] | Chinmayee B. Nagaraj[6] | Alyssa L. Rippert[7] | Catherine P. Schultz[8] | Elizabeth A. Ulm[6] | Niki Armstrong[2]

[1]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA

[2]Parent Project Muscular Dystrophy, Washington, District of Columbia, USA

[3]Department of Neurology, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

[4]Center for Genetic Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA

[5]Department of Pediatrics, University of Colorado School of Medicine, Children's Hospital Colorado, Aurora, Colorado, USA

[6]Division of Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA

[7]Division of Human Genetics, Department of Pediatrics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

[8]Ambry Genetics, Aliso Viejo, California, USA

Correspondence
Angela M. Pickart, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA.
Email: pickart.angela@mayo.edu

Abstract

The dystrophinopathies encompass the phenotypically variable forms of muscular dystrophy caused by pathogenic variants in the *DMD* gene. The dystrophinopathies include the most common inherited muscular dystrophy among 46,XY individuals, Duchenne muscular dystrophy, as well as Becker muscular dystrophy and other less common phenotypic variants. With increased access to and utilization of genetic testing in the diagnostic and carrier setting, genetic counselors and clinicians in diverse specialty areas may care for individuals with and carriers of dystrophinopathy. This practice resource was developed as a tool for genetic counselors and other health care professionals to support counseling regarding dystrophinopathies, including diagnosis, health risks and management, psychosocial needs, reproductive options, clinical trials, and treatment. Genetic testing efforts have enabled genotype/phenotype correlation in the dystrophinopathies, but have also revealed unexpected findings, further complicating genetic counseling for this group of conditions. Additionally, the therapeutic landscape for dystrophinopathies has dramatically changed with several FDA-approved therapeutics, an expansive research pathway, and numerous clinical trials. Genotype–phenotype correlations are especially complex and genetic counselors' unique skill sets are useful in exploring and explaining this to families. Given the recent advances in diagnostic testing and therapeutics related to dystrophinopathies, this practice resource is a timely update for genetic counselors and other healthcare professionals involved in the diagnosis and care of individuals with dystrophinopathies.

KEYWORDS
Becker muscular dystrophy, Duchenne muscular dystrophy, genetic counseling, genetic testing

1 | INTRODUCTION

This practice resource serves as a reference for genetic counselors and other healthcare professionals regarding best practices for genetic counseling specific to dystrophinopathies. In recent years, updated natural history data, the use of expanded carrier screening, and broadened treatment options have evolved our understanding of dystrophinopathies. The extreme variable expressivity and complex genotype–phenotype correlations, along with ever-evolving therapeutic options, make genetic counseling far more complicated than it has been in past years. This resource is a timely tool for use in practice.

Genetic counseling regarding dystrophinopathies may occur in a variety of settings and, therefore, this document is applicable to

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genetic counselors and healthcare providers caring for patients in a number of clinical areas. Genetic counseling may be part of the diagnostic evaluation in the pediatric or adult setting in general genetics, neurology, or cardiology clinics. Additionally, patients may be counseled in prenatal or pre-conception sessions due to a family history of dystrophinopathy or as a result of positive expanded carrier screening.

Our goal is to provide a resource to address the unique and complex aspects of genetic counseling for the collective dystrophinopathies. The information provided in this document related to clinical aspects, molecular testing, reproductive considerations, newborn screening, and treatment reflects the current knowledge of dystrophinopathies at the time of publication.

In this paper, we address the X-linked dystrophinopathies using gender-inclusive language (Cho et al., 2022). Specifically, we will refer to XX individuals (who will typically be assigned female sex at birth) and XY individuals (who will typically be assigned male sex at birth). We refer to carriers for a pathogenic *DMD* variant as heterozygous XX individuals and individuals with a dystrophinopathy as hemizygous XY individuals.

What is known about this topic?

There are extensive publications on the dystrophinopathies, including the genetic etiology, diagnosis, management, and treatment of Duchenne and Becker muscular dystrophy. There are fewer publications focused on carriers of dystrophinopathies.

What does this paper add to this topic?

This practice resource provides an up-to-date and comprehensive review of the dystrophinopathies for genetic counselors and other healthcare professionals. The most current dystrophinopathy topics relevant for genetic counselors are discussed in this one resource, including testing strategies and algorithms, expanded carrier screening and other reproductive considerations, *DMD* variant interpretation, and FDA-approved treatment options.

2 | METHODS

This practice resource represents the collective experience and opinion of a multi-center working group of board-certified genetic counselors from the United States with experience in the clinical care of individuals with dystrophinopathies and the laboratory-based molecular analysis of the *DMD* gene. It is based on the group's professional experience, a review of pertinent English-language medical articles, and other published expert consensus statements. The use of this practice resource is voluntary and is not intended to define a singular approach to genetic counseling of individuals with dystrophinopathies, but rather to highlight the key counseling aspects and unique considerations specific to this patient population. Genetic counseling, including that regarding the ethical and legal challenges in genetic counseling and testing, should always be guided by the overall ethical code of the National Society of Genetic Counselors (NSGC Code of Ethics, 1992/2017).

3 | BACKGROUND

3.1 | Clinical information

Dystrophinopathy refers to the form of muscular dystrophy caused by the reduction or absence of the dystrophin protein. The dystrophin protein is critical in maintaining the integrity of the muscle cell membrane, and its reduction or absence leads to muscle breakdown over time. The *DMD* gene is translated to produce the dystrophin protein, and most affected individuals have identifiable pathogenic or likely pathogenic variants in the *DMD* gene. For succinctness, the term pathogenic will be used throughout this document, but both likely pathogenic and pathogenic variants identified by molecular testing are actionable. The *DMD* gene is located on the X chromosome, and therefore dystrophinopathies follow X-linked inheritance with hemizygous XY individuals typically presenting with more severe clinical features. Primary manifestations of dystrophinopathies affect skeletal muscle, cardiac muscle, and the brain.

Historically, dystrophinopathies had two distinct clinical characterizations: the more severe presentation of Duchenne muscular dystrophy (DMD) and the milder presentation of Becker muscular dystrophy (BMD). However, it has been demonstrated over time that dystrophinopathies represent a larger spectrum of clinical phenotypes, including intermediate phenotypes between classic DMD and BMD as well as a form of dystrophinopathy limited to cardiomyopathy. The distinction between DMD and BMD has been further blurred with the shifting of the disorder's natural history, including prolonged ambulation and increased life span (Birnkrant, Bushby, Bann, Apkon, et al., 2018; Merlini et al., 2012). The use of expert consensus guidelines for the management of DMD and the early and consistent use of corticosteroids may play a role in this shift (Birnkrant, Bushby, Bann, Apkon, et al., 2018). The clinical descriptions in this manuscript are intended to define the classic DMD and BMD phenotypes, although we acknowledge that these phenotypes can overlap.

3.2 | Prevalence and incidence

The worldwide prevalence of DMD is approximately seven cases per 100,000 XY individuals, with an incidence of approximately 1 per 5000 XY births (Crisafulli et al., 2020; Mendell et al., 2012). Within the United States, the prevalence of DMD or BMD is approximately 1.4 per 10,000 XY individuals between the ages of

5–24 years, with DMD being three times more prevalent than BMD (Romitti et al., 2015). Among individuals 5–9 years of age, 1.92–2.48 per 10,000 XY individuals are affected with DMD or BMD (Zhang et al., 2021).

Recent population-based expanded carrier screening has identified a carrier frequency of 7.3 per 10,000 (Johansen Taber et al., 2022) suggesting the prevalence of purported pathogenic *DMD* variants may be higher than previously expected. However, it is not clear whether all variants reported as pathogenic on expanded carrier screening result in disease.

3.3 | Duchenne muscular dystrophy

The average age of diagnosis of DMD for hemizygous XY individuals is 4.1 years, but symptoms are first noted at 2.6 years, on average (Ciafoloni et al., 2009; The Duchenne Registry: Ten Year Report, 2019; Thomas et al., 2022). Hemizygous XY individuals with DMD initially present with developmental delays, most notably gross motor delays. At approximately age 3 or 4, the onset of proximal muscle weakness becomes clinically apparent as an abnormal, "waddling" gait, difficulties with climbing, calf pseudohypertrophy, and a positive Gower sign. A Gower sign is difficulty standing from a seated position on the floor secondary to proximal muscle weakness; often individuals need to "walk" their hands up their legs to stand. Calf pseudohypertrophy is described as false muscular appearance to the calf muscles secondary to fibrofatty replacement of the muscle tissue (Ciafoloni et al., 2009). These presenting symptoms will often lead to an assessment of serum creatine kinase (CK) which is dramatically elevated, often 100-fold above the upper limit of normal (Fequiere et al., 2008).

Global developmental delays are common in hemizygous XY individuals with DMD, although gross motor delays may be most apparent. A study of infants and young children with DMD using the Bayley III Scales of Infant Development demonstrated lower than average performance in both cognitive and language domains, in addition to the gross motor domain. As expected, gross motor scores declined with increasing age, while cognitive and language scores did not change significantly with age (Connolly et al., 2013). In one study assessing overall IQ in individuals with DMD, close to 30% had a full-scale IQ less than 70, and the mean full-scale IQ of the cohort was 84. In addition, learning disabilities, attention-deficit hyperactivity disorder (ADHD), autism, anxiety disorder, and obsessive–compulsive disorder are common comorbidities (Banihani et al., 2015; Darmahkasih et al., 2020).

Young hemizygous XY individuals with DMD ultimately enter a plateau phase of their disease course at around 7 years of age when the rate of muscle degeneration is equivalent to the rate of normal development (McDonald et al., 2013). Current care considerations recommend discussion of the use of corticosteroids at the time of diagnosis, rather than waiting until the plateau or decline phase, although age of initiation, regimen, side effect profile, and age at discontinuation varies by patient (Birnkrant, Bushby, Bann, Apkon, et al., 2018; Cowen et al., 2019). After the plateau phase, the rate of muscle degeneration is greater than the rate of normal development and progressive muscle weakness becomes more evident. Hemizygous XY individuals with DMD not treated with corticosteroids will lose the ability to ambulate by around 10–12 years. With corticosteroid use, loss of ambulation can be delayed by 1–2 years (Kim et al., 2015).

Progressive weakness in individuals with DMD impacts multiple organ systems, including pulmonary, skeletal, and cardiac. The impact of progressive weakness on the respiratory muscles and diaphragm significantly contributes to morbidity and mortality. Over time, individuals with DMD develop restrictive pulmonary disease with reduced ability to clear secretions, increased risk of pneumonia, hypoventilation, and ultimately respiratory failure (McDonald, Gordish-Dressman, et al., 2018). Common orthopedic issues in individuals with DMD include osteoporosis, joint contractures, and scoliosis, the latter of which can also adversely impact respiratory function (Apkon et al., 2018). Pulmonary issues correlate with severity of the muscular weakness, as may scoliosis and joint contractures. Long-term corticosteroid use has been demonstrated to slow respiratory disease progression and the need for scoliosis surgery (Koeks et al., 2017).

Dilated cardiomyopathy (DCM) is one of the leading causes of dystrophinopathy-related morbidity and mortality. Left ventricular involvement of DCM can include any combination of (a) dilation of the left ventricle, (b) decrease in ejection fraction/heart function, (c) left ventricular fibrosis or scarring, and (d) symptoms of a decrease in heart function, which is called heart failure (Bozkurt et al., 2016; Hershberger et al., 2018; Richardson et al., 1996). Left ventricular involvement can be identified by echocardiogram and cardiac MRI, but the diagnosis of left ventricular fibrosis requires MRI. Approximately one quarter of individuals with DMD have onset of DCM in the first decade of life, and over 90% of individuals with DMD over 18 years of age demonstrate left ventricular involvement (Nigro et al., 1990). Individuals with DMD can also exhibit left ventricular involvement at an early age, despite being asymptomatic. In addition, non-ambulatory patients may have little to no symptoms of heart failure despite severe left ventricular dysfunction (Nigro et al., 1990). Several studies have suggested delayed onset of cardiomyopathy and decreased rate of decline of cardiac function with corticosteroid use (Barber et al., 2013; McDonald, Henricson, et al., 2018).

In hemizygous XY individuals with DMD born after 1990, the median age at death is 28.1 years, most commonly due to cardiorespiratory failure (Broomfield et al., 2021). The age of survival has continued to increase over the years as aggressive ventilatory support and early cardiac medical therapy are implemented (Broomfield et al., 2021; Szabo et al., 2021).

3.4 | Becker muscular dystrophy

BMD has a wider range of clinical symptoms and is notably more variable than DMD. The classic BMD phenotype is similar to DMD,

but with later onset of muscle weakness and slower progression. Hemizygous XY individuals with classic BMD present with proximal muscle weakness predominantly affecting the hip girdle and thigh extensor at approximately age 10–13 years, which is later than hemizygous XY individuals with DMD. Children may have initial findings of muscle cramping with activity, gross motor delay, trouble climbing stairs and keeping up with peers during physical activity, or cognitive impairment. Muscle weakness progresses at a more gradual rate, with hemizygous XY individuals with classic BMD remaining ambulatory until after the age of 16 (Bello et al., 2016). HyperCKemia and calf pseudohypertrophy are also seen. Neuromuscular scoliosis can develop proportionately to muscle weakness. The mean age of DCM diagnosis in individuals with BMD is 14.5 years, similar to that of DMD (Connuck et al., 2008). DCM typically presents disproportionately to the degree of muscle involvement and may develop even in individuals with mild or minimal muscle involvement. Death is typically due to either cardiac dysfunction or pulmonary complications as a result of respiratory muscle weakness (Connuck et al., 2008; Passamano et al., 2012).

For individuals with non-classic BMD, muscle weakness may present throughout adulthood, and some may remain ambulatory throughout their lives. The spectrum of BMD has further expanded to include subclinical symptoms such as hyperCKemia with or without muscle cramping and pain, DCM, myoglobinuria/rhabdomyolysis, calf pseudohypertrophy, and autism/autistic-like features (Bello et al., 2016; Yazaki et al., 1999). The source of this variability may be a combination of the nature of the causative dystrophin variant, level of residual dystrophin protein expression, and genetic modifiers (Hoffman, 2020).

From a neuropsychological perspective, hemizygous XY individuals with BMD are more likely to have learning disabilities, behavioral problems, and/or autism than XY individuals in the general population (Young et al., 2008). Although studies have demonstrated a similar rate of at least one behavioral or emotional symptom in DMD versus BMD (73% and 77%, respectively), the average full-scale IQ in hemizygous XY individuals with BMD does not differ significantly from the population mean (Lambert et al., 2020; Young et al., 2008).

3.5 | Heterozygous 46,XX individuals (previously known as female carriers)

XX individuals who are heterozygous for pathogenic *DMD* variants frequently exhibit variable symptoms associated with dystrophinopathies, ranging from manifesting carriers to a mild and/or subclinical presentation. Historically, the term manifesting carrier was reserved for those XX individuals with clinical symptoms similar in severity to DMD and/or BMD, but many clinicians believe that all heterozygous XX individuals exhibit symptoms to some extent.

All heterozygous XX individuals are at risk for cardiomyopathy, including peripartum cardiomyopathy. The onset of cardiac involvement occurs in adulthood and the penetrance increases with age (Ishizaki et al., 2018). Exact risks are uncertain and vary by age, method of assessment, and definition of involvement. In studies conducted in 2016 and 2020, up to 49% of heterozygous XX individuals had at least one positive finding on cardiac MRI (characterized by decreased left ventricular ejection fraction and/or left ventricular fibrosis) by age 44 and 41, respectively, suggesting a subclinical process (Florian et al., 2016; Mah et al., 2020). A recent study of 53 adult heterozygous XX individuals found that a majority had structural or functional cardiac involvement as demonstrated by echocardiogram (62%) or cardiac MRI (49%). This same study identified that over 70% have one or more ECG abnormalities (Solheim et al., 2021). The prevalence of unequivocal DCM among heterozygous XX individuals has been estimated to be between 7 and 17% (American Academy of Pediatrics Section on Cardiology and Cardiac Surgery, 2015; Ishizaki et al., 2018).

Heterozygous XX individuals may also have neuromuscular symptoms which, in some cases, progress over time. Common symptoms include muscle weakness (which may be asymmetric), myalgias, cramping, calf hypertrophy, and fatigue. The variability of symptoms in heterozygous XX individuals may be a result of skewed X chromosome inactivation, the specific *DMD* variant, or modifier genes (Soltanzadeh et al., 2010). A recent study measuring muscle strength using isokinetic dynamometry found weakness greater than two standard deviations from the control mean in 40% of heterozygous XX individuals. Additionally, 81% of heterozygous XX individuals had either reduced muscle strength or increased muscle fat fraction as determined by muscle MRI (Fornander et al., 2021). CK levels in heterozygous XX individuals may be elevated, but there is significant variability, and levels tend to normalize with increasing age. However, symptomatic XX individuals generally have higher CK levels (Mah et al., 2020; Percy et al., 1979; Zhong et al., 2019).

Fewer heterozygous individuals have a severe presentation like classic DMD or BMD in XY individuals. A number of genetic mechanisms result in more severely affected XX individuals, including skewed X-inactivation, Turner syndrome, X chromosome abnormalities, and biallelic pathogenic variants (Bushby et al., 1993; Fujii et al., 2009; Jacobs et al., 1981; Sano et al., 1987). The true prevalence of severely affected manifesting heterozygous XX individuals is difficult to determine. Different studies have defined manifesting or symptomatic in different ways, with manifesting carriers estimated to account for 2.5–19% of heterozygous XX individuals (Ishizaki et al., 2018). Studies that include broader symptoms such as muscle cramping or muscle weakness have generally identified a larger number of symptomatic heterozygous XX individuals (Fornander et al., 2021; Norman & Harper, 1989; Soltanzadeh et al., 2010). Neuropsychiatric differences in heterozygous XX individuals have not been well studied.

3.6 | X-linked dilated cardiomyopathy

An additional dystrophin-deficient phenotype is X-linked DCM, where hemizygous XY individuals present with early-onset DCM

in the absence of skeletal muscle disease. Reported heterozygous XX individuals present with later onset, milder phenotypes. This phenotype is believed to be rare, and the prevalence and mortality rates are unknown. These individuals can also have elevated CK. Onset occurs in the second or third decade of life and mortality typically results from either heart failure or ventricular arrhythmias (Nakamura, 2015). It can be difficult to clinically distinguish between X-linked DCM and mild BMD depending on age and method of evaluation, and both phenotypes may present within the same family (Nakamura, 2015). Precise genotype–phenotype correlations differentiating BMD from X-linked DCM and predicting cardiac severity for all dystrophinopathies are not fully understood; however, this is an emerging field of research (Nakamura, 2015; Zhou et al., 2021).

4 | REPRODUCTIVE CONSIDERATIONS

Traditionally, the dystrophinopathies were considered to follow an X-linked recessive pattern of inheritance, but over time it has become clear that heterozygous XX individuals can have a clinical phenotype; thus, an X-linked pattern of inheritance is a more appropriate descriptor. Heterozygous XX individuals have a 25% chance to have a hemizygous XY child with dystrophinopathy with each pregnancy and a 25% chance to have a heterozygous XX child who is a carrier. More severe DMD phenotypes appear to follow Haldane's rule, with approximately one-third of cases resulting from a de novo pathogenic variant and two thirds of cases resulting from an inherited *DMD* variant from a heterozygous XX parent. The likelihood of being a carrier is increased to 90% for the heterozygous XX parent of hemizygous XY individuals with less severe phenotypes (Lee et al., 2014). Given the X-linked pattern of inheritance, a hemizygous XY parent with dystrophinopathy will pass on the *DMD* variant to all XX offspring (who will be carriers) and no XY offspring.

The dystrophinopathies are associated with a significant risk of germline mosaicism. This was initially discovered in 1987 when the condition was transmitted to more than one affected XY offspring of a XX parent who did not have evidence of being a carrier via molecular testing in white blood cells (Bakker et al., 1987). The historically reported recurrence risk for transmission of the pathogenic *DMD* variant to any offspring (XY or XX) due to germline mosaicism was 14–20% (Bakker et al., 1989; van Essen et al., 1992). Recent data confirms a 7% risk for transmission of a pathogenic *DMD* variant to XY offspring (Helderman-van den Enden et al., 2009). Germline mosaicism poses a significantly increased recurrence risk in apparently de novo cases where the recurrence risk would generally be considered to be very low. For this reason, heterozygous XX parents of a child with dystrophinopathy who test negative for a *DMD* variant via blood or saliva remain at an increased risk over the general population to have a child with a dystrophinopathy and should be made aware of all reproductive options. XX individuals who have a sibling with a *DMD* variant should consider genetic testing to determine carrier status even if the parents of the affected individual had negative *DMD* testing via blood or saliva.

TABLE 1 Points to consider—reproductive considerations.

- To maximize reproductive options, individuals at risk for offspring with dystrophinopathy should pursue molecular analysis and genetic counseling prior to conception or as early as possible in gestation. They should be educated regarding all available reproductive options
- Prenatal and/or pre-conception genetic counseling should include a tailored discussion of the natural history of dystrophinopathies. If appropriate, genetic counselors should offer connection to other families and appropriate resources and support specific to DMD/BMD
- All pregnant persons or individuals considering pregnancy who carry a pathogenic *DMD* variant, including those identified during pregnancy, should be referred for cardiology evaluation
- Relevant at-risk relatives should be counseled about the possibility of germline mosaicism
- Carriers and families considering preimplantation genetic testing-monogenic (PGT-M) should be referred to a genetic counselor with specific expertise in assisted reproductive technologies

In order to maximize reproductive options, individuals at risk to have children with dystrophinopathy should be offered genetic counseling and molecular analysis prior to conception or as early as possible in gestation (see Table 1). Given the variability of CK elevation in heterozygous XX individuals and the nonspecific nature of CK elevation in general, CK assessment is not a reliable assay to determine carrier status (Fornander et al., 2021). Individuals should be educated regarding all available reproductive options, including unassisted pregnancy with no testing, traditional prenatal diagnostic procedures (chorionic villus sampling and amniocentesis), preimplantation genetic testing following in vitro fertilization, and other alternative options such as donor egg or sperm or adoption.

Preimplantation genetic testing for monogenic/single-gene disorders (PGT-M) may be an option for individuals at risk to have a child with dystrophinopathy. However, PGT-M may be complicated depending on the specific *DMD* variant. PGT-M for deletions and duplications often requires phasing to prevent misdiagnosis as a result of allele dropout or other technical challenges. Phasing requires data from another family member in the direct line (parent or child of the carrier; in some cases, fetal tissue from past pregnancies can be used). If a heterozygous XX individual has a de novo pathogenic deletion or duplication variant and no children, or no family members available for testing, PGT-M may not be possible. In some cases, PGT-M can be performed for sequence variants without phasing. Given the costs and complexities of this testing, PGT laboratories may be unable or unwilling to perform PGT-M for potential germline mosaicism, until such mosaicism has been demonstrated by the birth of another child with the pathogenic variant (De Rycke & Berckmoes, 2020).

In instances where PGT-M cannot be performed or is not desired, but a *DMD* variant is known, prenatal diagnosis would remain an option, as a fetus can be tested via chorionic villus sampling (CVS) or amniocentesis for the familial variant. PGT-Aneuploidy (PGT-A) for sex selection may also be considered to preferentially select XX embryos to reduce the likelihood to have a symptomatic child. In the United States at the time of publication, non-invasive prenatal

testing (NIPT) for dystrophinopathies is not available, although NIPT for other single-gene disorders is possible (Mohan et al., 2022; Zhang et al., 2019). In addition, NIPT is sometimes used to predict fetal sex and, if the results indicate that the fetus is 46,XY, the pregnant person could pursue CVS or amniocentesis.

5 | MOLECULAR MECHANISMS

The *DMD* gene is located at Xp21.2-p21.1. The *DMD* locus was discovered in 1986 aided by breakpoint analysis in a number of 46,XX individuals with X; autosome translocations presenting with DMD-like phenotypes (Jacobs et al., 1981; Kimura et al., 1986; Nevin et al., 1986). *DMD* is an extremely large gene spanning over 2 Mb with 79 exons, which has complicated genetic testing efforts.

DMD encodes the dystrophin protein, which includes an actin-binding amino terminus, rod domain, cysteine-rich domain, and carboxy terminus (Tinsley et al., 1993). Dystrophin is an integral cytoplasmic component of the dystrophin-glycoprotein complex which plays a critical role in muscle membrane stability. Pathogenic variants in *DMD* result in loss of or reduced dystrophin protein expression, rendering muscle cells prone to contraction-induced muscle degeneration over time.

The dystrophin protein has three full length isoforms, each with 79 exons, but with differing first exons and promoters (see Figure 1). The brain isoform, Dp427b, is expressed in the cortical neurons and hippocampus of the brain. The Purkinje isoform, Dp427p, is associated with cerebellar Purkinje cell expression and low-level skeletal muscle expression. The muscle isoform, Dp427m, is primarily expressed in skeletal and cardiac muscle. Several additional internal promoters drive expression of smaller protein products, such as Dp140 and Dp71 (Muntoni et al., 2003). The complex nature of dystrophin gene isoform expression can impact genotype–phenotype correlations based on the location of the corresponding pathogenic variant and impact to specific isoform expression (Muntoni et al., 2003). For example, Dp140 and Dp71 are expressed in the fetal brain and pathogenic variants affecting these isoforms are associated with neurodevelopmental conditions such as autism spectrum disorder, attention-deficit hyperactivity disorder, and cognitive impairment. The correlation between the Dp71 isoform (exons 63–79) and cognitive impairment has been well documented (Daoud et al., 2009; Darmahkasih et al., 2020; Doorenweerd et al., 2017).

The majority of individuals with dystrophinopathies have a large deletion or duplication of at least one exon within the *DMD* gene; however, a variety of other variant types have been reported including nonsense, missense, and splice site variants, small deletions and insertions, and more complex genomic rearrangements. Data from locus-specific mutation databases indicates that approximately 70% of individuals with dystrophinopathies have single or multi-exonic deletions, 10% have single or multi-exonic duplications, and 20% have small sequence variants (Bladen et al., 2015; Tuffery-Giraud et al., 2009). Missense variants are estimated to account for only 1%–4% of pathogenic variants associated with the dystrophinopathies. The variant spectrum varies by phenotype, however. The majority of pathogenic variants in DMD and BMD are whole exon deletions, 61% and 81%, respectively. There is an increased frequency of small sequence variants and duplications in individuals with DMD, 26% and 13%, as compared to individuals with BMD, 13% and 6% (Tuffery-Giraud et al., 2009). Hotspots for both deletions and duplications involve exons 3–7 and exons 45–55 (Tuffery-Giraud et al., 2009).

The expression of dystrophin drives genotype–phenotype correlation in the dystrophinopathies with complete absence of dystrophin protein corresponding to a severe, DMD phenotype and residual expression associated with a milder, BMD phenotype. Although exceptions exist, the correlation of genotype to phenotype for gross deletions and duplications in the dystrophin gene depends on the impact to the reading frame. The juxtaposition of the exons adjacent to the deletion or duplication can be used to infer if the reading frame will be impacted. Deletions and duplications

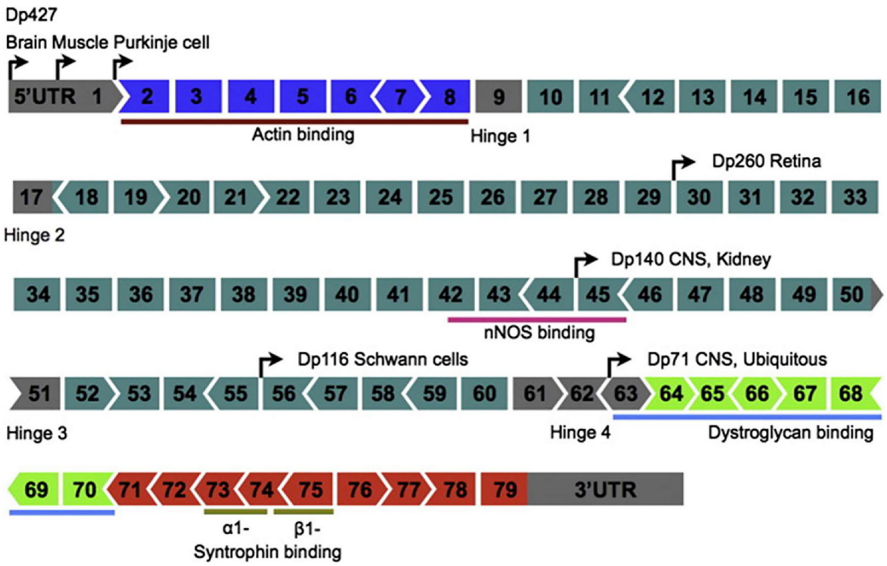

FIGURE 1 Structure of the *DMD* gene, including positions of promoters for different isoforms. Reprinted from "Splicing therapy for neuromuscular disease," by A. Douglas and M. Wood, 2013, Molecular and Cellular Neurosciences, 56, p. 169. Copyright 2013 by Elsevier, open access.

that shift the reading frame will typically result in the creation of a premature stop codon and likely result in nonsense-mediated mRNA decay, leading to a complete absence of dystrophin protein production. Deletions and duplications that are predicted to preserve the reading frame will generally allow for residual dystrophin protein production associated with a milder phenotype. Of note, some in-frame deletions and duplications result in the creation of a novel termination codon at the newly created exon-exon junction; therefore, these in-frame lesions may still result in nonsense-mediated decay. Both the amount and content of residual dystrophin protein expression are important for determining phenotype, but exceptions to the reading frame rule can complicate genotype–phenotype predictions as discussed in the Pitfalls in Interpretation section.

6 | LABORATORY INVESTIGATIONS/ DIAGNOSTIC CONFIRMATION

6.1 | Indications for testing

Laboratory investigations for dystrophinopathies are typically initiated by a neurologist or geneticist once a child has been referred by their pediatrician or primary care provider (PCP). Often the presenting symptoms include muscle weakness, delayed motor milestones, difficulty running and climbing stairs, and toe walking. Clinicians may also observe calf pseudohypertrophy, a Gower maneuver, and elevated transaminases. Many young children have been diagnosed with dystrophinopathy after the initial finding of elevated transaminases discovered incidentally, perhaps in conjunction with evaluation of a viral illness. Usually the pediatrician/PCP will order a serum CK level as the first test since this is a simple, inexpensive test. Hemizygous XY individuals with DMD/BMD will have dramatically elevated serum CK levels of >2000 IU/L; however, CK is nonspecific and elevated CK levels within the range of approximately 500–1200 IU/L may be indicative of other neuromuscular disorders or non-neuromuscular conditions (Moghadam-Kia et al., 2016). An elevated CK usually prompts a referral to neurology and/or genetics (Aartsma-Rus et al., 2019). Other indications for testing include developmental delay, cardiomyopathy, and positive family history.

6.2 | Molecular versus non-molecular testing

In the past, muscle biopsies were typically performed on all children with suspected dystrophinopathy. Dystrophin immunohistochemical staining could be performed to quantify the amount of dystrophin present, with most hemizygous XY individuals with DMD having completely absent dystrophin whereas hemizygous XY individuals with BMD having variable or residual dystrophin present. However, since molecular techniques have advanced, muscle biopsies have become less common and in most cases are not needed to confirm a diagnosis of DMD/BMD (Birnkrant, Bushby, Bann, Apkon, et al., 2018). A muscle biopsy is still helpful in cases where the clinical presentation is intermediate, or the anticipated phenotype is unclear. This allows for quantification of residual dystrophin expression which can provide prognostic information and inform treatment decision making. The muscle sample can be tested for the presence of dystrophin protein by immunohistochemistry of tissue cryosections or by western blot of a muscle protein extract (Birnkrant, Bushby, Bann, Apkon, et al., 2018).

6.3 | Molecular testing

The earliest genetic testing for dystrophinopathies was performed using linkage analysis; however, once the *DMD* gene was isolated, testing of the actual *DMD* gene replaced this indirect methodology. Testing strategies in the 1990s were limited to multiplex PCR and Southern blot, and only some whole exon deletions and duplications in the hotspot regions could be identified. Newer methods such as multiplex ligation-dependent probe amplification (MLPA) and microarray-based comparative genomic hybridization (array-CGH) became standard to detect deletions and duplications across the entire *DMD* gene, and Sanger sequencing allowed for the detection of smaller variants, but these were often performed sequentially due to cost (Hamed & Hoffman, 2006; Nallamilli et al., 2014).

With the advent of next-generation sequencing (NGS), testing for DMD/BMD can now be done in one comprehensive assay to detect whole exon deletions and duplications (copy number variants or CNVs), as well as smaller sequence variants (Table 2). Depending on the laboratory used, NGS can detect deep intronic sequence variants. Determining the significance of such variants is challenging at this time and laboratories may not report all deep intronic variants (Nallamilli et al., 2021). Most large laboratories in the United States are offering NGS for the *DMD* gene, but some laboratories are still using the two-tiered approach to testing. Financial barriers to genetic testing have virtually been eliminated with the development of sponsored testing programs in the United States.

As outlined above, testing using older technologies may not provide accurate results. Updated molecular testing should be undertaken to ensure the *DMD* variant is appropriately characterized (see Figure 2).

6.4 | Testing strategies

A number of different diagnostic tests are available for the dystrophinopathies, and the ideal approach to testing should be individualized based on the indication. Given the complexities of both test selection and interpretation of results, laboratory-genetic counselors are an excellent resource throughout the testing process.

If the diagnosis of a dystrophinopathy is strongly suspected, an NGS-based assay is an appropriate first-line test (see Figure 3). The phenotype of dystrophinopathies overlaps with a multitude of other muscular dystrophies and a large NGS muscular dystrophy multi-gene panel may be indicated for individuals with atypical

presentations. A multi-gene cardiomyopathy panel, which includes *DMD*, should be considered for individuals presenting with isolated cardiomyopathy phenotypes.

Ideally, carrier screening due to family history of a known dystrophinopathy should be undertaken with a targeted test for the specific causal variant in the family (see Figure 4). In the absence of a known causal variant, testing can be complex and should be performed in the context of genetic counseling given the limitations in interpretation of a negative result. For example, the affected family member may have an undetectable *DMD* variant, or they may be affected with another condition that clinically mimics dystrophinopathy.

In the setting of a positive family history, there is no clear consensus on when carrier testing should be ordered for an asymptomatic XX family member. Traditionally, the recommendation for genetic testing in an individual at risk for an adult-onset condition was to wait until adulthood (Botkin et al., 2015; Friedman Ross et al., 2013). However, determining carrier status prior to pregnancy is optimal. Because many pregnancies are unplanned, carrier testing prior to sexual activity is reasonable. This testing should include conversations with both the individual who is at risk and guardians (if the individual is a minor).

Some families prefer to determine carrier status at a younger age, in order to enable early discussions and avoid testing during the teen years, when social pressures are especially difficult. Historically, testing of minors for carrier status has been discouraged (American Academy of Pediatrics Committee on Bioethics, Committee on Genetics and the American College of Medical Genetics and Genomics Social, Ethical, and Legal Issues Committee, 2013). However, given the increased identification of carrier status through NBS and incidental findings in expanded genetic testing methods, such as chromosome microarray and exome or genome sequencing, some researchers theorize that early disclosure can allow for education at developmentally appropriate times, and therefore integration into their lives at an early age (VanNoy et al., 2019).

TABLE 2 Points to consider—genetic testing.

- Genetic testing is the gold standard for diagnosing dystrophinopathies as it is more accessible, more cost effective and less invasive than a muscle biopsy
- The approach to genetic testing should be based on the patient's indication (see figures)
- Updated molecular testing should be performed for individuals with a clinical diagnosis and past negative testing as well as patients with a molecular diagnosis using outdated or imprecise methodologies. Updated molecular testing is needed for clinical trial enrollment and drug therapy amenability
- Clinicians must exercise caution when reviewing DMD reports that do not provide sufficient evidence for the classification of the variant, especially in the absence of a family history

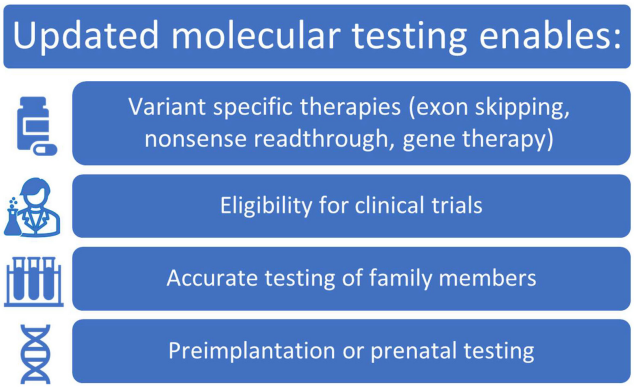

FIGURE 2 Benefits of updated *DMD* molecular testing. © 2024 National Society of Genetic Counselors. All rights reserved.

6.5 | Newborn screening

Newborn screening for DMD has been piloted in a number of countries and is typically based on elevated CK on dried blood spots followed by confirmatory genetic testing (Mendell & Lloyd-Puryear, 2013). Past pilots showed that newborn screening was generally effective at identifying XY individuals with DMD (Mendell et al., 2012). Pilots in several states, utilizing the FDA-authorized Creatine Kinase-Muscle isoform test kits (CK-MM) followed by *DMD* genetic testing, have been conducted to provide evidence in

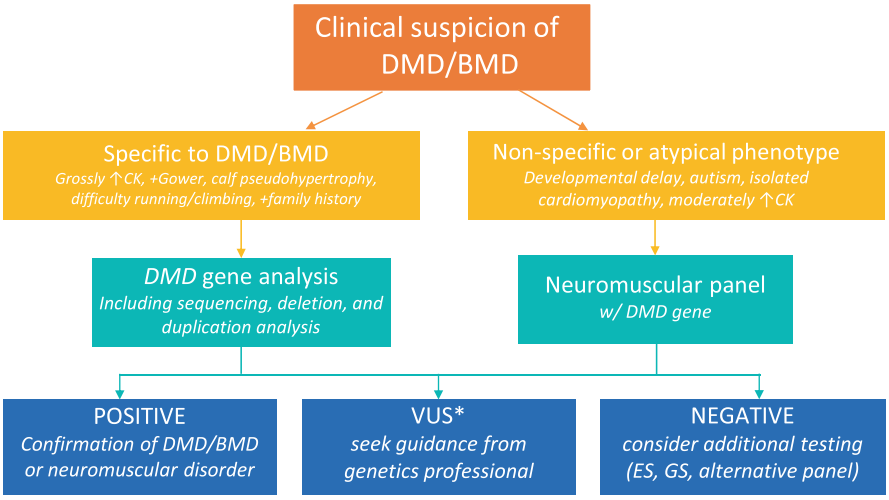

FIGURE 3 Testing Algorithm for Individuals with a clinical suspicion of DMD/BMD. *See Strategies to Clarify the Significance of a DMD Variant table. ES, exome sequencing; GS, genome sequencing. © 2024 National Society of Genetic Counselors. All rights reserved.

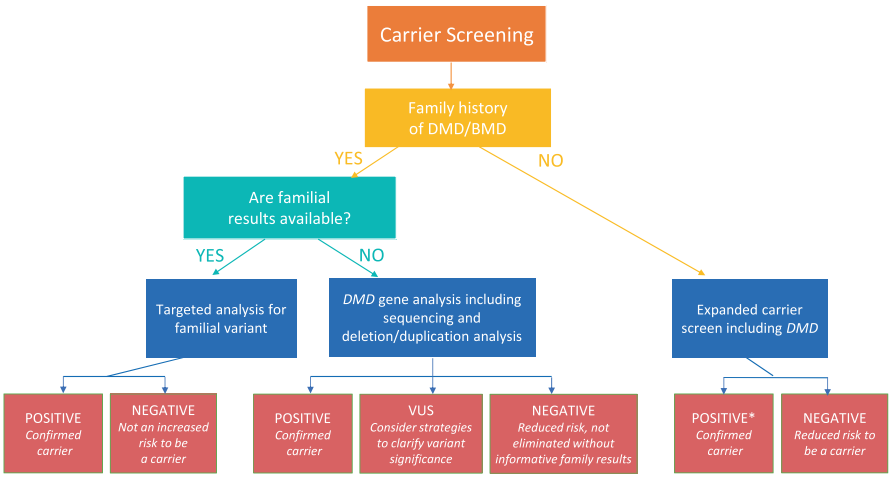

FIGURE 4 Carrier screening algorithm. *See Special Considerations for Expanded Carrier Screening. © 2024 National Society of Genetic Counselors. All rights reserved.

TABLE 3 Variants frequently reported to result in a broad phenotype[a].

Variant	Predicted frame status	DMD	BMD	X-linked DCM	Asx
Nonsense variants in exon 1		X	X	X	X
Del exon 3–7	OF	X	X		
Del exon 45	OF	X	X		
Del exon 45–51	IF	X	X		
Del exon 48	IF	X	X	X	
Del exon 49–51	IF	X	X	X	X
Dup exons 56–61	OF	X			X

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Abbreviations: asx, asymptomatic; del, deletion; dup, duplication; IF, in-frame; OF, out-of-frame.

[a]This list includes frequently reported examples but is not all-inclusive. Expanded carrier screening and resulting cascade testing may identify additional variants in asymptomatic individuals; this list may expand over time.

support of adding DMD to the Recommended Uniform Screening Panel (RUSP), and several states, including New York and Ohio, have mandated newborn screening for DMD at the time of this publication (Parad et al., 2021; Tavakoli et al., 2023). Please see Table S1 for details on the benefits and limitations of DMD newborn screening.

6.6 | Pitfalls in interpretation

The ability to provide a molecular diagnosis in individuals with dystrophinopathies has increased dramatically with the advent of comprehensive NGS-based *DMD* genetic testing. The large size of the *DMD* gene, however, coupled with the complex phenotypes associated with dystrophinopathies, makes variant interpretation challenging.

Accurate laboratory classification of *DMD* variants requires comprehensive review of all available data points including the predicted impact to the reading frame, the presence of the variant in individuals in general population databases such as gnomAD, and the presence of the variant in individuals with dystrophinopathies in the medical literature, global mutation databases (HGMD, ClinVar), and gene-specific mutation databases (Richards et al., 2015). Genetic counselors at laboratories and advocacy organizations specializing in DMD can assist with access to internal data and/or large databases which can provide additional information to help clarify the significance of *DMD* variants. Clinicians should be cautious while reviewing reports, particularly when sufficient evidence justifying the classification has not been provided. The presence of *DMD* variants in general population databases does not rule out pathogenicity given the complex nature of age- and sex-related penetrance and mild phenotypes (isolated hyperCKemia) associated with dystrophinopathies. Furthermore, the presence of the variant in the literature and mutation databases does not ensure the variant is pathogenic as this is dependent on the quality of the data provided. Muscular dystrophies are genetically heterogeneous, many with shared clinical manifestations, so identification of a variant in *DMD* does not prove direct causation.

In addition to the inherent challenges to *DMD* variant interpretation, there are many examples of variants that do not follow expected genotype–phenotype correlations, including exceptions to

the reading frame rule. Data from the Leiden mutation database suggest exceptions to the reading frame rule occur approximately 9% of the time, but a more recent study specific to individuals with BMD detected out-of-frame deletions and duplications in 30% of their cohort (Aartsma-Rus et al., 2006; Kesari et al., 2008). For example, out-of-frame deletions of exons 3–7 sometimes result in a BMD phenotype, while in-frame deletions of exon 3 can occur in patients with a DMD phenotype (Tuffery-Giraud et al., 2009). The 5′ and 3′ regions of the gene are known hotspots for exceptions to the reading frame rule. In addition, BMD patients appear to have more exceptions to the reading frame rule (Kesari et al., 2008).

Several additional genotype–phenotype exceptions exist related to the dystrophinopathies (see Table 3). Pathogenic variants that are reported as identical can result in two different phenotypes, and this has been documented for many deletions and duplications (Takeshima et al., 2010). It is important to recognize that, depending on the methodology employed, deletions and duplications reported as identical may not involve the exact same coding sequence. Relatively large lesions have been associated with milder phenotypes, including in a family with nearly half of the coding sequence deleted (England et al., 1990; Nakamura et al., 2008). Additionally, large duplications extending beyond the 5′ or 3′ ends of the gene may not disrupt production of a normal protein product.

Nonsense variants have been reported in a number of individuals with a BMD phenotype, including a recurrent nonsense variant in exon 1, due to exonic point mutation induced exon skipping or use of alternative initiation codons (Flanigan et al., 2009, 2011; Torella et al., 2020). Torella et al. provides a helpful resource on exon-specific genotype/phenotype correlation of nonsense variants across *DMD* (Torella et al., 2020).

6.7 | Special considerations for expanded carrier screening

DMD is currently included on many universal carrier screening panels. In their 2021 update, the American College of Medical Genetics and Genomics (ACMG) recommended including *DMD* on expanded carrier screens. Data from Myriad Women's Health and The Duchenne Registry suggest that a significant portion of identified heterozygous XX individuals have in-frame deletions or duplications (typically associated with BMD), which is in contrast to expected prevalence data (Armstrong et al., 2021).

Interpretation of *DMD* variants identified outside of the setting of a personal or family history of a dystrophinopathy, as in the case of expanded carrier screening (ECS), can be particularly difficult (Armstrong et al., 2021; Rudd et al., 2019). Population-based molecular testing for the dystrophinopathies has resulted in an increased awareness regarding the extreme clinical variability of dystrophinopathies and complex nature of variant interpretation for *DMD* gene variants. Details regarding the variant may be limited, or conflicting, making it challenging to assess the pathogenicity of the variant and provide accurate counseling regarding the anticipated phenotype. Expanded carrier screening may result in the identification of variants of unclear phenotypic significance and/or severity, which may lead to patient anxiety and confusion regarding appropriate reproductive risks and options (Mastantuoni et al., 2018). Genetic counseling in the setting of such variably-reported phenotypes is particularly difficult; however, genetic counselors have specific expertise and skill in communicating uncertainty in these scenarios.

There are several anecdotal and published reports documenting cases where a presumed pathogenic variant (often in-frame deletions or duplications, splice site variants, or missense variants) identified as part of carrier screening has been later identified in asymptomatic or mildly affected XY relatives, suggesting the variant is either benign or associated with mild disease (Chin et al., 2021). For example, a fairly large duplication of exons 10–27 has been identified in an asymptomatic 16-year-old XY individual with normal serum CK, muscle histology, and dystrophin expression on muscle biopsy and in healthy adult XY individuals (Brison et al., 2019; Nicolau et al., 2021). A recent report describes two families with the same duplication of exons 56–61, one presenting with classic DMD and the other with asymptomatic XY individuals. In the former case, the duplication was proven in direct tandem orientation, while the latter was found to be an insertional duplication outside of, and therefore not disrupting, the *DMD* gene (Bai et al., 2022). Additionally, a given deletion may be associated with widely varying phenotypes, such as deletion of exons 49–51, which has been reported in individuals with DMD, BMD, isolated DCM, and asymptomatic XY individuals (Kapoor et al., 2012; Kaspar et al., 2009; Lim et al., 2020; Rudd et al., 2019; Ulm et al., 2023). Genetic counseling for the more severe DMD phenotype in the setting of a variant sometimes associated with mild or no disease could result in incorrectly informed reproductive decision making.

Individuals identified as having a *DMD* pathogenic variant via ECS should have genetic counseling, which should include a review of available data regarding the specific variant identified and any genotype–phenotype correlations. Results should be correlated with the patient's clinical and family history. In the absence of a family history of symptoms, genetic counselors and other healthcare providers should exercise extreme caution in the interpretation of results and counseling of patients. It is important to review the inherent challenges in predicting potential phenotypes given the significant phenotypic variability, and intrafamilial variability, associated with dystrophinopathies and the documented exceptions to expected genotype–phenotype correlations. If possible, it can be helpful to pursue additional testing to help clarify the significance of results as reviewed below.

6.8 | Clarifying negative or uncertain molecular results

Although genetic testing allows for the detection of a specific molecular diagnosis in a majority of individuals with a dystrophinopathy, there remain individuals who carry variants that escape detection with even the most up-to-date methodologies. This includes

individuals who carry variants that fall outside the assay region of interest, or who carry a VUS, particularly missense variants and non-canonical splice variants (see Figure 5). Approximately 2% or fewer patients with a clinical diagnosis of DMD/BMD will test negative for a pathogenic *DMD* variant (Nallamilli et al., 2021). Muscle biopsy can be helpful in these cases to confirm a diagnosis and assess the level of dystrophin protein. RNA sequencing of muscle tissue can aid in molecular diagnosis of individuals with variants that escape detection and/or reporting by conventional DNA sequencing methods (Waldrop et al., 2022). RNA sequencing can also be very helpful in determining the functional impact of splice site variants on correct RNA splicing (Nallamilli et al., 2021; Okubo et al., 2016).

In cases where a VUS is identified, segregation analysis can be performed to determine if the variant segregates with the condition. Co-segregation of the condition in other affected individuals consistent with an X-linked pattern of inheritance provides supportive data toward pathogenicity. The presence of the variant in unaffected adult XY individuals suggests the variant may be benign. It is important to thoroughly evaluate XY individuals with the variant, ideally by a neurologist and cardiologist with dystrophinopathy expertise, as they may have mild or subclinical symptoms suggesting the variant may be pathogenic but associated with mild symptoms.

6.9 | Laboratory investigation of XX individuals suspected to have dystrophinopathy

Diagnostic testing for symptomatic heterozygous XX individuals should be similar to the testing done for XY individuals. This includes serum CK level and, in the setting of a family history of a dystrophinopathy, *DMD* analysis to identify a disease-causing variant. XX individuals without a family history of dystrophinopathy may benefit from a neuromuscular gene panel to assess for both dystrophinopathies and other neuromuscular disorders that present with a similar phenotype. A muscle biopsy may be helpful for some patients. X-inactivation studies have been used in the past to assess for skewed X-inactivation in XX individuals, but may not be informative on blood and are not routinely ordered (Apkon et al., 2021).

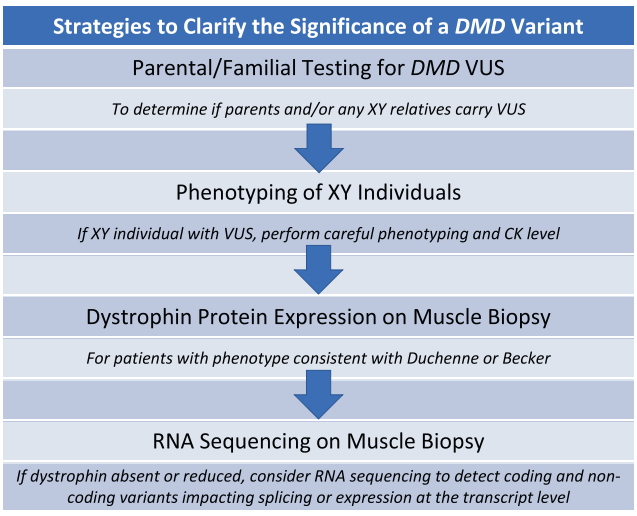

FIGURE 5 Strategies to clarify the significance of a *DMD* variant. © 2024 National Society of Genetic Counselors. All rights reserved.

7 | MANAGEMENT OF INDIVIDUALS WITH DYSTROPHINOPATHY

Genetic counselors are integral members in the holistic care of all individuals with dystrophinopathies and should be familiar with the care guidelines (Table 4). Genetic counselors have the unique skills of providing complex medical and genetic information in a way that can be understood by individuals of all educational backgrounds while addressing the psychosocial needs of the family. This education is critical for the parents of a newly diagnosed child to understand the clinical aspects, inheritance, prognosis, and management of dystrophinopathies.

7.1 | Duchenne muscular dystrophy

Appropriate management of individuals with dystrophinopathies has been shown to prolong survival and improve quality of life (Birnkrant, Bushby, Bann, Alman, et al., 2018; Birnkrant, Bushby, Bann, Apkon, et al., 2018; Birnkrant, Bushby, Bann, Apkon, Blackwell, et al., 2018). Typically, a neuromuscular specialist acts as the lead clinician within a multi-disciplinary team that includes specialists from cardiology, pulmonology, nutrition management, physical therapy and rehabilitation, orthopedics, psychology, and genetics. Expert consensus guidelines regarding the management of individuals with dystrophinopathies have been put forth by the DMD Care Considerations Working Group (Birnkrant, Bushby, Bann, Alman, et al., 2018; Birnkrant, Bushby, Bann, Apkon, et al., 2018; Birnkrant, Bushby, Bann, Apkon, Blackwell, et al., 2018). These guidelines provide a standard of care for individuals with dystrophinopathies. For the purposes of this resource, a high-level overview of management considerations will be provided here, but for further details, the consensus guidelines should be reviewed.

In addition to management strategies related to extending ambulation, mobility, and independence as long as possible, proactive management for cardiac disease and lung disease is crucial. Late identification of pulmonary and cardiac disease can lead to poor clinical outcomes. For more information regarding screening management and symptom management, please refer to the published DMD consensus guidelines.

7.2 | Becker muscular dystrophy

There are no current standard of care guidelines available for BMD patients. There is limited data on the efficacy of corticosteroid

TABLE 4 Points to consider—utilization of genetic counseling services.

- All newly diagnosed patients, and their family members, should receive genetic counseling services as part of their care plan. Ideally this would include both pre- and post-test counseling. Genetic counseling for newly diagnosed patients and families should cover the specific *DMD* variant identified, X-linked inheritance and recurrence risks, testing for at-risk relatives, and an overview of the natural history and prognosis for dystrophinopathies and available support and education resources
- As diagnostic, reproductive and therapeutic options related to DMD/BMD may have high costs and barriers to access, genetic counselors should inform all individuals of available options to eliminate potential biases related to socioeconomic status and promote health equity
- All individuals identified as having a *DMD* pathogenic variant via expanded carrier screening should receive genetic counseling given the complexities of variant interpretation in population-based screening and the subsequent education required regarding the results
- Consider utilizing genetic counselors based in a laboratory specializing in *DMD* testing or genetic counselors based in an advocacy organization focused on DMD for additional expertise

treatment, and therefore there are no formal recommendations on its use in treatment of BMD (King et al., 2007). Individuals with BMD may be followed similarly to those with DMD depending on their presentation and needs. Proactive management for cardiac and pulmonary disease remains critical. As pulmonary issues correlate to degree of muscle weakness, pulmonary surveillance may take place at a less frequent rate as per physician discretion.

7.3 | Heterozygous XX individuals

For heterozygous XX individuals, cardiac surveillance should begin by age 25 and include imaging at least every 5 years, unless disease is identified which would result in more frequent surveillance (Birnkrant, Bushby, Bann, Alman, et al., 2018). Workup should include electrocardiogram and non-invasive imaging, such as echocardiogram or cardiac MRI when available. Evaluation is best performed by cardiologists familiar with dystrophin-cardiomyopathy (American Academy of Pediatrics Section on Cardiology and Cardiac Surgery, 2015). Research is ongoing to better understand exact risk and how to best screen and follow heterozygous XX individuals.

Heterozygous XX individuals should undergo evaluation for cardiomyopathy ideally prior to conception or soon after a pregnancy is realized. Pregnancy is known to increase one's risk for cardiac sequelae given the increased blood volume and cardiac load. This is not unique to dystrophinopathies, but a known consequence of pregnancy in patients with or at risk for cardiomyopathy (Ishizaki et al., 2018; Schaufelberger, 2019). Those with evidence of cardiomyopathy should be monitored and managed by a cardiologist and a high-risk obstetrician (Lee & Judge, 2017).

Neurology evaluation for heterozygous XX individuals experiencing neuromuscular symptoms is best performed by providers familiar with dystrophinopathy. Depending on phenotype and history, additional studies may be considered to clarify whether symptoms are related to the *DMD* variant or have another etiology. Additional studies may include genetic testing for other neuromuscular conditions, CK, serial CKs, and muscle biopsy. X-inactivation studies on muscle biopsy can also be considered (Gruber et al., 2022). Heterozygous XX individuals with symptoms consistent with DMD may be treated with corticosteroids as well as exon skipping or nonsense-readthrough therapies, especially if the individual has a concurrent diagnosis of Turner syndrome (45,X). Referral to physical and occupational therapy is often helpful to heterozygous XX individuals with symptoms.

8 | TREATMENT

As discussed previously, genetic counselors work as part of a collaborative, multi-disciplinary team. Although genetic counselors do not manage the treatment of individuals with dystrophinopathies, a familiarity with treatment modalities can be helpful for discussions with patients and families in collaboration with the treating physicians, especially given the number of FDA-approved variant-specific therapies (Table 5).

8.1 | Corticosteroids

The treatment of choice for DMD, especially for children between the ages of 5 to 15 years, is corticosteroid therapy, which has been shown to improve muscle strength and function, delay loss of ambulation, and slow the decline of pulmonary function and the development of cardiomyopathy (McDonald, Henricson, et al., 2018; Szabo et al., 2021). A prospective cohort study that followed patients for up to 10 years found that patients who had a year or longer of corticosteroid treatment had increased median age at loss

TABLE 5 Points to consider—treatment and resources.

- Individuals with DMD should be managed using the published consensus guidelines. There are no consensus guidelines specific to BMD at this time. Aspects of the DMD care guidelines may be applicable to individuals with BMD, particularly those related to cardiac and pulmonary care
- Heterozygous XX individuals are at increased risk for cardiac and neuromuscular manifestations of dystrophinopathies. Cardiac evaluation is recommended for all heterozygous XX individuals in early adulthood. Any heterozygous XX individual of any age with neuromuscular symptoms should be referred to neurology for thorough evaluation
- At the time of publication there are five FDA-approved therapies for DMD, four of which are DMD variant-specific. The neuromuscular care team, including genetic counselors, should have familiarity with available therapies, which will increase in number over time, and how to determine their patient's amenability to variant-specific therapeutics
- Patients should be referred to a neuromuscular specialist for discussion of applicable clinical trials

of mobility milestones by 2.1–4.4 years and upper limb milestones by 2.8–8.0 years as compared to patients with <1 month of glucocorticoid treatment (McDonald, Henricson, et al., 2018). Dosing of corticosteroids is variable with daily and twice-weekly dosing most often prescribed in the USA. Long-term corticosteroids can have significant adverse effects, with increased risks of short stature, delayed puberty, obesity, immunosuppression, osteoporosis, adrenal crisis if abruptly discontinued, cataracts, and behavioral and mood disturbances. A novel corticosteroid with reduced side effects, vamorolone, was recently approved by the FDA (Guglieri et al., 2022).

8.2 | Exon skipping therapies

As of March 2023, there are four FDA-approved exon skipping therapies available for DMD: eteplirsen (exon 51 skipping, approved in 2016), golodirsen (exon 53 skipping, approved in 2019), casimersen (exon 45 skipping, approved in 2021), and viltolarsen (exon 53 skipping, approved in 2020). These therapies received accelerated approval based on increased dystrophin expression demonstrated on muscle biopsy and are considered standard of care for eligible patients (Takeda et al., 2021). They are approved for all patients with an amenable pathogenic variant, typically large deletions of at least one exon, with no age restriction. 30% of the total DMD population is expected to be eligible for one of these drugs, which are given as weekly intravenous infusions (Aartsma-Rus et al., 2009; Bladen et al., 2015). Antisense oligonucleotides are used to bind to an exon adjacent to the deletion. The oligonucleotide binding results in targeted pre-mRNA splicing out of the selected exon to restore the reading frame, resulting in a truncated, yet in-frame dystrophin protein (see Figure 6). A number of tools exist to determine exon skipping eligibility, including DOVE (dmd.nl). Some very large deletions or deletions involving the actin-binding domain or dystroglycan binding domain may not benefit from exon skipping, as the protein produced may remain non-functional.

Evaluation of patients with naturally occurring genetic variants that allow for the production of low levels of dystrophin suggests that even small amounts of dystrophin expression result in delayed progression of disease, including loss of ambulation (de Feraudy et al., 2021). This suggests that therapies that result in even small increases in dystrophin levels may improve outcomes. As the low levels of dystrophin expression with these naturally occurring variants are congenital, it is expected that earlier initiation of therapies could provide increased benefits.

Exon skipping therapies also show a cumulative effect, with a progressive increase in the amount of dystrophin as measured by western blot and by dystrophin positive fibers over a 2-year period (McDonald et al., 2021). The currently approved exon skipping therapies produce generally low levels of dystrophin, which has been demonstrated to slow disease progression but has not been shown to halt disease. Please see Table S2 for additional details on currently approved exon skipping therapies.

Exon skipping therapies are generally well-tolerated (Takeda et al., 2021). Labels for these therapies contain precautions for hypersensitivity reactions and a potential for kidney toxicity based on animal data. Challenges exist regarding insurance coverage, such as coverage exclusions or limitations to certain age groups and ambulatory statuses (Margaretos et al., 2022). Pharmaceutical company patient support programs are available to assist patients and families with access and coverage.

Exon skipping therapies are being developed for several additional *DMD* exons. The development pathway is based on the frequency of amenable variants, such that the greatest number of individuals with DMD may benefit. In addition, the development of next-generation exon skipping therapies is underway. These aim to increase efficiency of exon skipping and, therefore, dystrophin quantity.

8.3 | Nonsense readthrough

Ataluren is an oral drug previously approved by the European Medicines Agency (EMA) and multiple other countries outside of the USA for hemizygous XY individuals who are 2 years and older who carry a pathogenic premature stop variant in *DMD*. It is not currently approved in the USA, although it may be available through clinical trials. Approximately 10%–15% of hemizygous XY individuals with DMD have a nonsense variant and are therefore eligible for this treatment. Readthrough or suppression of the nonsense variant stop signal allows for the production of some dystrophin protein. Please see Table S2 for additional data on ataluren treatment.

8.4 | Gene therapy

Gene replacement therapy has been an especially active topic of research. As of writing this manuscript, there are ongoing Phase 3 clinical trials in gene therapy. Because of the size of the *DMD* gene and the limitations of currently available vectors, the gene therapies all utilize micro or mini-dystrophin constructs (Elangkovan & Dickson, 2021). Each company's construct is slightly different. Some data suggest that patients who have certain genetic variants may be at risk for an immune response to the micro or mini-dystrophin, as they have no endogenous exposure to those sections of the dystrophin protein. Consequently, both Phase 3 trials have limitations of which pathogenic variants can participate in the trials. It is unclear if those patients excluded from trials will ultimately be eligible for gene therapy. In addition, patients with pre-existing antibodies to the adeno-associated viral vector may also be ineligible for gene therapy, again because of risk of immune response. Gene therapy also has significant risks, with two reported deaths in DMD-related clinical trials (Lek et al., 2023; Philippidis, 2022).

Delandistrogene moxeparvovec-rokl was approved by the FDA in June 2023 for ambulatory individuals with DMD who are ages 4 and 5 years. This therapy was approved through the

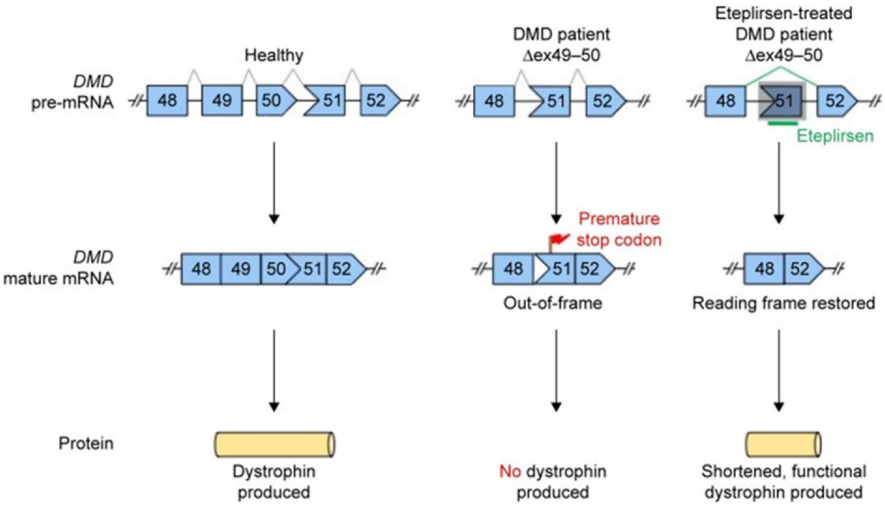

FIGURE 6 Mechanism of an exon skipping therapeutic. Comparison of RNA splicing in a healthy individual versus a patient with an out-of-frame *DMD* deletion 49–50 and the same patient on eteplirsen, an exon 51 skipping therapeutic that restores the reading frame. Drug Design, Development and Therapy 2017, 11, 533–545 Originally published by and used with permission from Dove Medical Press Ltd.

accelerated approval pathway based on an increased production of microdystrophin and is given as a single dose intravenous infusion. Delandistrogene moxeparvovec-rokl is contraindicated in individuals with any deletion, whole exon or or single/multiple nucleotide(s), of exons 8 and/or 9 of the *DMD* gene, as individuals with deletions in this region appear to be at higher risk for an immune response. In addition, individuals must have anti-AAVrh74 total binding antibody titers that are less than 1:400 (Sarepta Therapeutics, Inc. ELEVIDYS (delandistrogene moxeparvovec-rokl)[package insert] U.S. Food and Drug Administration https://www.fda.gov/media/169679/download).

Delandistrogene moxeparvovec-rokl results in the production of a microdystrophin that is similar to those found in families with a late-onset Becker. It is not expected to be curative, and the duration of treatment is unclear. The four individuals initially treated showed functional improvements and sustained stabilization at 4 years post-dose (O'Rourke et al., 2023), with individuals in more recent trials showing stabilization of functional outcomes at 2 years post-dose (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10366687/). Clinical trials in additional age groups are ongoing, with the potential for treatment of younger and older individuals in the future.

8.5 | Ongoing clinical trials

As of writing this manuscript, there is a robust drug development pathway for dystrophinopathies. Patients and their families should be educated about all available options for clinical trials and research studies. Many of these therapies are variant-specific, hence the need for a confirmed molecular diagnosis, which may warrant up-to-date genetic testing. However, many investigational therapies are not variant-specific and therefore could potentially benefit all patients, regardless of their *DMD* variant. Providers should have a discussion with the family regarding the pros and cons of clinical trial participation and should give a clear explanation of the difference between investigational therapies and approved therapies. Genetic counselors can be particularly useful with these conversations given their expertise. In addition, there are a number of ongoing clinical trials specific to BMD, and some potential therapies for DMD may also be effective in BMD.

Investigational therapies represent a broad variety of therapeutic approaches, from increasing/replacing dystrophin to combating fibrosis to restoring cellular energy. A number of next-generation exon skipping therapies are also in process. Some of these are for exons not currently available, while others hope to improve upon the efficacy of exon skipping therapies that are already available. Clinical trials can be located at ClinicalTrials.gov (https://clinicaltrials.gov/) and the WHO International Clinical Trials Registry Platform (https://www.who.int/clinical-trials-registry-platform).

9 | PSYCHOSOCIAL ASPECTS OF DYSTROPHINOPATHIES

The initial diagnosis of dystrophinopathy can be very overwhelming for families, given the complexity and gravity related to the diagnosis, inheritance, and management of the disease. The psychosocial aspects should not be overlooked and should be discussed with the family at the time of diagnosis and re-visited as a child with dystrophinopathy progresses in their disease course (Table 6). Just as individuals with dystrophinopathies need ongoing medical management, social and emotional care is also imperative and should extend to caregivers and other family members. Healthcare providers should discuss when and how to explain the diagnosis to the affected child, as well as siblings, taking into consideration each unique family situation. Open family communication and age-appropriate conversations about all aspects of the diagnosis are critical for childrens' identity, coping and future decision making (Plumridge et al., 2010; Sulmonte et al., 2021).

As with many X-linked inherited conditions, it is not uncommon for heterozygous XX individuals to feel guilt, shame or remorse related to the transmission of the familial pathogenic variant to their child. These feelings should be addressed and normalized

TABLE 6 Points to consider—psychosocial aspects.

- The psychosocial aspects of dystrophinopathy should be discussed with the family at the time of diagnosis and re-visited frequently due to the progressive nature of symptoms
- Carrier parents may feel guilt, shame or remorse related to the transmission of the pathogenic variant to their child, and these feelings should be addressed and normalized by healthcare providers
- A psychosocial management plan for patients with dystrophinopathy is essential for their well-being and must extend throughout their life span, given the significant burden of coping with a chronic and progressive disease
- Healthcare providers should consider referring patients and families to local support groups and national advocacy organizations (see list below)

by healthcare providers. Given the psychological burden, some heterozygous XX individuals may benefit from speaking to a mental health provider (Birnkrant, Bushby, Bann, Apkon, Blackwell, et al., 2018).

All caregivers, regardless of carrier status, are at risk for caregiver burnout given the substantial emotional and physical burden of caring for a child with DMD. Caregiving in DMD has been associated with impaired health-related quality of life, poor sleep quality, reduced family function, depression, pain, stress, sexual dysfunction, and lower self-esteem, as well as a considerable impact on work life and productivity (Jackson et al., 2021; Landfeldt et al., 2018).

A psychosocial management plan for patients with dystrophinopathy is essential for their well-being, given the significant burden of coping with a chronic and progressive disease. Detailed recommendations specific to the psychosocial management of dystrophinopathy are available (Colvin et al., 2018). Young patients with dystrophinopathy may begin to develop sadness or feelings of exclusion or isolation in the early phases of disease when they are not able to keep up with their peers. This is further complicated by the increased risk for cognitive and behavioral issues. In a recent study of patients with dystrophinopathy, approximately 32% of patients had ADHD, 19% to 27% had an intellectual disability, and 15% had autism spectrum disorder (ASD) (Banihani et al., 2015). Increased rates of anxiety and depression are also observed in patients with dystrophinopathies (Latimer et al., 2017).

As adults, XY individuals with dystrophinopathy have to adjust to life with a progressive disease and the accompanying impact on daily living. It can be psychologically distressing to think about end-of-life care and how they wish to experience the end of life in regard to medical management and preparations for affairs. Palliative care addresses the physical, emotional, psychosocial, and spiritual needs of patients nearing the end of life and may benefit individuals with DMD. Studies suggest that there is a need to improve awareness and provision of palliative care services for DMD (Arias et al., 2011; Corpuz Tapawan et al., 2020).

It is now recognized that psychosocial management of patients with dystrophinopathy is necessary across the entire life span.

TABLE 7 Points to consider—resources.

Patient resources
• CureDuchenne: www.cureduchenne.org • Duchenne Family Assistance Program: https://littleherculesfoundation.org/family-assistance-program/ • Jett Foundation: www.jettfoundation.org • Muscular Dystrophy Association (MDA): www.mda.org • Parent Project Muscular Dystrophy (PPMD): www.parentprojectmd.org • TREAT-NMD: www.treat-nmd.org
DMD-specific variant databases
• *DMD*-Open Access Variant Explorer (DOVE – reading frame and exon skipping prediction tool): www.dmd.nl/DOVE • Duchenne Registry (International DMD/BMD Registry with curated genotype–phenotype data): www.duchenneregistry.org • Leiden Open Variation Database (LOVD): https://databases.lovd.nl/shared/genes/DMD • Universal Mutation Database (UMD): www.umd.be/TREAT_DMD/

Although once viewed as ancillary to managing the significant medical needs of patients with dystrophinopathy, it is now standard practice to integrate psychosocial management into the multidisciplinary management of dystrophinopathies. Advances in psychosocial management will reduce the burdens on the patient and family and improve their quality of life (Colvin et al., 2018). Healthcare providers should consider referring patients and families to local support groups and national advocacy organizations, which can provide education, support, and a sense of community (Plumridge et al., 2012; Tesei et al., 2020).

10 | RESOURCES

Genetic counselors based at DMD advocacy organizations often have extensive experience in all aspects of dystrophinopathies and are available to assist healthcare providers, patients, and families. This can include reviewing genetic test reports, discussing amenability to therapies, providing clinical trial and research study options, and assisting with additional testing for the patient or other family members. In addition, they often have access to large databases, such as The Duchenne Registry, which can provide additional information to assist with *DMD*-variant classification (see Table 7).

Genetic counselors at advocacy organizations can provide additional education and support directly to patients and families by offering recommendations for clinics and providers with expertise in dystrophinopathies. They can also connect patients and families with other dystrophinopathy families on the local or national level and offer ways to get involved either in-person or virtually.

DMD-specific variant databases can be accessed for data related to the frequency of specific variants and genotype–phenotype data. See Table 7 for a list of patient and variant-specific resources.

11 | CONCLUSION

The availability of comprehensive molecular testing, further understanding of the wide clinical spectrum, increased uptake of population-based screening, and rapidly evolving discovery of molecular-based therapies has increasingly shed light on the complex nature of dystrophinopathies. These complexities make counseling individuals and families with dystrophinopathies uniquely challenging. The appropriate education and care of individuals with dystrophinopathies and their families requires a multidisciplinary team, with genetic counselors being an integral member. This resource is a tool to provide comprehensive background information regarding all aspects of the provision of genetic counseling for this unique patient population.

AUTHOR CONTRIBUTIONS

Angela M. Pickart, Ann S. Martin, Brianna N. Gross, and Niki Armstrong lead the development and coordination of the manuscript. Chinmayee B. Nagaraj, Elizabeth A. Ulm, Brianna N. Gross, and Niki Armstrong developed and wrote content related to clinical aspects and management. Angela M. Pickart, Ann S. Martin, and Catherine P. Schultz developed and wrote content related to the molecular aspects and genetic testing. Leslie M. McCallen, Alyssa L. Rippert, and Lisa M. Dellefave-Castillo developed and wrote content related to cardiology. All authors contributed substantially to the conception or design of the work, drafting, and/or critically revising the work. All authors provided final approval of the draft to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICT OF INTEREST STATEMENT

NSGC requires systematic evidence review, practice guideline, and practice resource authors to complete a conflict of interest (COI) disclosure survey annually, starting at the formation of the author group. Authors must also report interim COI changes to the NSGC Practice Guideline Committee (PGC) within 30 days. The PGC categorizes COI into two tiers. Tier 1 COI includes any direct, personal financial benefit that is ongoing or within the previous 12 months from a commercial entity that may benefit from the document. Tier 1 COI includes research funding from a commercial entity for 25 percent or greater of an author's salary. Tier 2 COI includes limited consultant roles, paid stipends/travel, and ongoing consultancy roles with companies that are involved in healthcare but may not directly benefit from the document. The PGC assesses the overall balance of COI for the author group and requires that no more than 40 percent of authors have Tier 1 COI, and no more than 80 percent have either Tier 1 or Tier 2 COI. Lead authors must be free of Tier 1 COI for the entirety of the development of the document and can only have Tier 2 COI if serving alongside a co-lead author with no Tier 1 or Tier 2 COI. Author Ann Martin is employed by Parent Project Muscular Dystrophy (PPMD) and a portion of her salary is funded through PPMD's Decode Duchenne program, sponsored by Sarepta Therapeutics, PTC Therapeutics, Vertex Pharmaceuticals, and NS Pharma. Author Ann Martin has received funding from Sarepta Therapeutics and PTC Therapeutics for work on advisory committees. Author Niki Armstrong is employed by PPMD and a portion of her salary is funded through PPMD's Newborn Screening Initiative, sponsored by Pfizer, Sarepta Therapeutics, PTC Therapeutics, and Solid Biosciences. Author Brianna Gross is employed by The Children's Hospital of Philadelphia and her position is funded by the Muscular Dystrophy Association, and she has received funding from Novartis for a speaking engagement. Author Catherine Schultz is employed by Ambry Genetics. Author Angela Pickart, Lisa Dellefave-Castillo, Leslie McCallen, Chinmayee Nagaraj, Alyssa Rippert, and Elizabeth Ulm declare that they have no conflicts of interest to disclose.

ETHICS STATEMENT

Human studies and informed consent: This practice resource did not include human subject research.

Animal studies: No non-human animal studies were carried out by the authors for this article.

DISCLAIMER

This practice resource (PR) is provided by the National Society of Genetic Counselors (NSGC) solely to serve as a helpful practice management resource and tool for genetic counselors and other healthcare providers. NSGC's PRs are not evidence-based; instead, they are based on the personal recommendations and experience of the authors. Each NSGC PR focuses on a clinical or practice-based issue, includes points for the genetic counselor or other healthcare provider to consider, and is based on the author(s) review and analysis of current professional literature believed to be reliable. As such, the information provided and ideas discussed in NSGC's PRs (i) reflect only the current scientific and clinical knowledge at the time of publication; (ii) are only current as of their publication date; and (iii) are subject to change without notice as advances emerge. PRs do not (and are not intended to) dictate an exclusive course of management nor guarantee a particular outcome. NSGC's PRs are never intended to displace a genetic counselor or other healthcare provider's best medical judgment based on the clinical circumstances of a particular patient or patient population. NSGC publishes PRs for educational and informational purposes only and does not "approve" or "endorse" any specific methods, practices, or sources of information contained therein.

PGC EXTERNAL REVIEW

The practice resource manuscript underwent external peer review through the standard peer-review process at the *Journal of Genetic Counseling*. In addition, a draft of the manuscript was reviewed and

critically appraised by the NSGC membership, the NSGC Practice Guidelines Committee, the NSGC Ethics Advisory Group, NSGC Legal, and the NSGC Board of Directors. The PR author group's lead author(s) revised the manuscript in response to external peer-review comments and those from the above NSGC reviews. Changes to the PR were required to be unanimously accepted by the full PR author group.

ORCID

Angela M. Pickart https://orcid.org/0009-0004-3105-3372

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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