

## Corporate Medical Policy

### Genetic Testing for Duchenne, Becker, Facioscapulohumeral, Limb-Girdle Muscular Dystrophies AHS – M2074

**File Name:** genetic\_testing\_for\_duchenne\_becker\_facioscapulohumeral\_limb\_girdle\_muscular\_dystrophies  
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#### Description of Procedure or Service

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Muscular dystrophies, genetic conditions characterized by progressive muscle atrophy, can be caused by several genetic mutations. Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are due to mutations to the dystrophin gene on the X chromosome (Darras, 2020a). Facioscapulohumeral muscular dystrophy (FSHD) occurs due to a contraction of the polymorphic macrosatellite repeat D4Z4 on chromosome 4q35 (Darras, 2020b).

Duchenne muscular dystrophy (DMD), the more severe of the dystrophin-related muscular dystrophies, typically presents in males during their toddler years. Patients with DMD rarely survive beyond their thirties due to respiratory insufficiency or cardiomyopathy. Unlike DMD, Becker muscular dystrophy (BMD) is less severe and typically presents in the teen years or adulthood; moreover, patients with BMD usually survive beyond thirty years of age (Darras, 2018a, 2020a).

In Facioscapulohumeral muscular dystrophy (FSHD), an autosomal dominant disorder, the contraction of the macrosatellite repeat D4Z4 results in an inappropriate expression of the *DUX4* (double homeobox protein 4) gene, which alters chromatin structure. FSHD has also been linked to DNA hypomethylation. Symptoms include muscle weakness in the face, arms, legs, abdomen, and scapula with a variable age of onset; however, 90% of patients are affected by the age of 20. Disease progression is slower than DMD with a normal or near-normal life span (Darras, 2018b, 2020b).

The limb-girdle muscular dystrophies (LGMDs) are a group of more than 30 rare hereditary progressive neuromuscular disorders (Murphy & Straub, 2015) characterized by predominantly proximal distribution of weakness in the pelvic and shoulder girdles. LGMDs result from mutations in genes required for normal muscle function and vary in severity, phenotype, pathology, and age of onset (Darras, 2018c).

#### Related Policies

[Genetic Testing For Inherited Cardiomyopathies and Channelopathies AHS – M2025](#)

[Whole genome and Whole Exome Sequencing AHS – M2032](#)

[General Genetic Testing, Germline Disorders AHS – M2145](#)

[General Genetic Testing, Somatic Disorders AHS – M2146](#)

**\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

#### Policy

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# Genetic Testing for Duchenne, Becker, Facioscapulohumeral, Limb-Girdle Muscular Dystrophies AHS – M2074

**BCBSNC will provide coverage for genetic testing for Duchenne, Becker, facioscapulohumeral and limb-girdle muscular dystrophies when it is determined the medical criteria or reimbursement guidelines below are met.**

## Benefits Application

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

## When Genetic Testing for Duchenne, Becker, Facioscapulohumeral and Limb-Girdle Muscular Dystrophies is covered

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1. Genetic testing for DMD gene mutations is considered medically necessary under the following conditions:
  - A. In individuals with signs and symptoms of a dystrophinopathy in order to confirm the diagnosis and direct treatment.
  - B. For at-risk female relatives: (At-risk females are defined as first- and second-degree female relatives and include the proband's mother, female siblings of the proband, female offspring of the proband, the proband's maternal grandmother, maternal aunts and their offspring).
    - i. To confirm or exclude the need for cardiac surveillance
    - ii. For preconception testing to determine the likelihood of an affected offspring in a woman considering a pregnancy
2. Genetic testing for facioscapulohumeral muscular dystrophy is considered medically necessary to confirm a diagnosis in a patient with clinical signs of the disease.
3. Genetic testing for mutations associated with limb-girdle muscular dystrophy (LGMD) to confirm a diagnosis of LGMD is considered medically necessary when signs and symptoms of LGMD are present but a definitive diagnosis cannot be made without genetic testing, and when the results of testing may lead to changes in clinical management that improve outcomes (e.g., confirming or excluding the need for cardiac surveillance) or genetic testing will allow the affected patient to avoid invasive testing, including muscle biopsy.
4. Genetic testing for mutations associated with limb-girdle muscular dystrophy (LGMD) in the reproductive setting is considered medically necessary when:
  - A. There is a diagnosis of LGMD in one or both of the parents, AND
  - B. Results of testing will allow informed reproductive decision making.
5. Genetic testing for mutations associated with LGMD is considered medically necessary in an asymptomatic individual to determine future risk of disease when both the following criteria (A & B) are met:
  - A. The individual has:
    - i. A close relative (i.e., first- or second-degree relative) with a known mutation consistent with LGMD; OR

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- ii. A close relative (i.e., first- or second-degree relative) diagnosed with LGMD whose genetic status is unavailable.
- B. Results of testing will lead to changes in clinical management (e.g., confirming or excluding the need for cardiac surveillance).

## **When Genetic Testing for Duchenne, Becker, Facioscapulohumeral and Limb-Girdle Muscular Dystrophies is not covered**

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1. Genetic testing for DMD gene mutations is considered investigational in all other situations.
2. Genetic testing for facioscapulohumeral muscular dystrophy is considered investigational for all other indications.
3. Genetic testing for mutations associated with LGMD is considered investigational in all other situations.

## **Policy Guidelines**

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### **Background**

#### **Duchenne Muscular Dystrophy (DMD) and Becker Muscular Dystrophy (BMD)**

Dystrophinopathies are due to mutations in the *DMD* (Dystrophin) gene located on the X-chromosome inherited in a recessive pattern. All hemizygous males will exhibit the characteristic phenotype whereas heterozygous females for a pathogenic mutation may exhibit a range of clinical manifestations. If skeletal muscles are affected, dystrophinopathies are classified as either DMD or BMD; however, if cardiac muscle is primarily affected, it is characterized as *DMD*-associated dilated cardiomyopathy (DCM) (Darras, Urion, & Ghosh, 2018).

DMD, the more severe phenotype of the skeletal muscle dystrophinopathies, typically presents in males before the age of five with progressive, symmetric muscle weakness and calf hypertrophy. Affected males are typically wheelchair-dependent before their teens, and the individual rarely survives beyond their thirties due to respiratory complications and heart failure. BMD is often less severe and manifests later in affected individuals at thirty years of age. Most of these individuals remain ambulatory into adulthood, with some reported to remain ambulatory as late as their sixties. Although skeletal muscle deterioration progresses more slowly in BMD, cardiomyopathy is the most common cause of death in these patients, shortening the life expectancy to the mid-forties. Many BMD patients receive heart transplants within five years after diagnosis of cardiomyopathy (Darras et al., 2018).

DMD or BMD should be suspected in males with elevated serum creatine phosphokinase (CK) levels (>10-times of normal and >5-times of normal, respectively) and clinical symptoms of dystrophinopathy. As permeability of the sarcolemma increases due to muscle damage, creatine phosphokinase is released beyond the normal range, which can be used as a diagnostic value. In DMD, CK levels are highest from two-to-five years of age. As the disease progresses, dystrophic muscle fibers begin to decay and the rate of CK release decreases (Kim et al., 2017). Hemizygous female carriers can also exhibit elevated serum CK levels, which are 2-10 times that of the normal range. (Darras et al., 2018).

#### **Clinical Validity and Utility of DMD/BMD Genetic Testing**

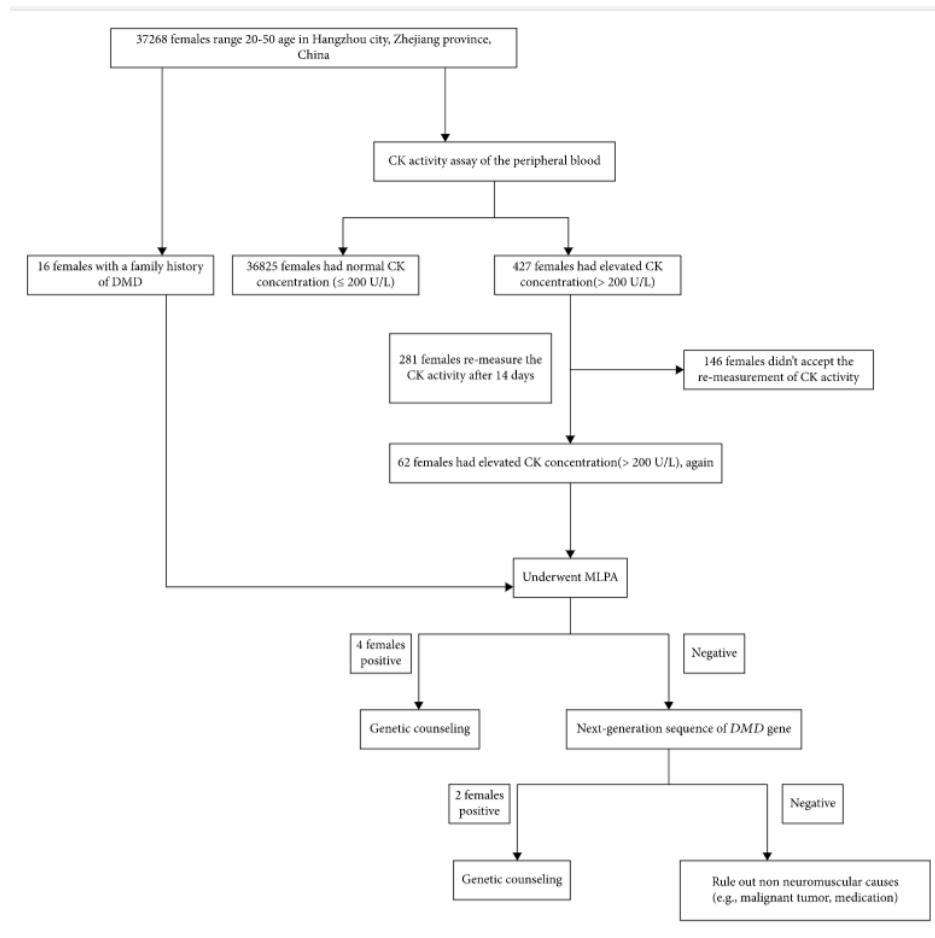
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A recent Chinese study of 146 at-risk pregnancies in 131 DMD families report a 99% mutation detection rate using “a prenatal diagnosis algorithm for dystrophinopathies that combines multiplex ligation-dependent probe amplification (MLPA), quantitative PCR, sequencing and linkage analyses” (H. Wang et al., 2017). This data also shows that 51.1% of the probands had de novo exon deletions. Recombination of the *DMD* gene occurred in 9 of the 146 pregnancies. The authors conclude that “the present results demonstrate the importance of considering maternal germline mosaicism in the genetic assessment. Prenatal diagnosis should be suggested to the parent with a DMD proband whether carrier testing found the causative mutation in the mother's blood or not (H. Wang et al., 2017).” The reported accuracy rate of this multiplex/quantitative PCR-based method is considerably higher than the reported accuracy rate (>70%) of a real-time PCR assay of the *DMD* gene (Zhang et al., 2013).

MLPA-based genetic testing of dystrophinopathies has been reported in many studies with varying degrees of sensitivity. A large study of 1053 Chinese DMD/BMD patients using MLPA testing reported identifying 70.56% of the probands (Yang et al., 2013) whereas a smaller study of 121 individuals (both male and female) reports confirmation of only 63% of patients and symptomatic females (Luce et al., 2016). A third study of using an algorithm of mPCR and MLPA on 150 male patients reported a 75% confirmation rate (Murugan, Chandramohan, & Lakshmi, 2010). Another study using MLPA concluded that “the reading-frame rule held in 90% to 94% of children, which is consistent with reports from other parts of the world. However, testing by MLPA is a limitation, and advanced sequencing methods including analysis of the structure of mutant dystrophin is needed for more-accurate assessments of the genotype-phenotype correlation (Vengalil et al., 2017).”

In a study by Han and colleagues, 37,268 females of reproductive age were recruited in Hangzhou, China, to identify definite DMD carriers prior to or early in pregnancy. Participants were screened for high CK activity (>200 U/L), a typical finding in 50-70% of asymptomatic heterozygous female DMD carriers (Brandsema & Darras, 2015), and DMD family history. The screening process narrowed down the number of participants for DMD genetic sequencing performed with Multiplex Ligation-Dependent Probe Amplification (MLPA) to detect gross deletions and duplications and Next-Generation Sequencing (NGS) based on Multiplex PCR to detect the small point mutations, insertions, and deletions. From the 37,268 participants, 427 females were identified to have CK levels above 200 U/L and 16 females with a previous family history of DMD. 427 females with high CK levels were asked to repeat CK testing, to which 281 females agreed, and 62 females showed to have sustained elevated serum CK levels. The 16 participants with DMD family history and 62 females with sustained CK levels >200 U/L were asked to undergo *DMD* genetic testing. “MLPA and NGS of the *DMD* gene identified 6 definite DMD carriers with clear pathogenic variants (3 of the 16 subjects with positive family history and 3 of the 62 subjects with negative family history) ... Four cases had deletions and/or duplications of *DMD* gene, mostly located in a hotspot mutation region (exons 44-55), one case carried a previously reported pathogenic missense variant, and a novel deleterious frameshift pathogenic variant was found in one case (Han et al., 2020).” Results of the screening for DMD carriers are summarized in the figure below (Han et al., 2020).

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Confirmed carriers of DMD pathogenic variant were provided professional genetic counseling and several reproductive choices such as preimplantation genetic diagnosis, prenatal genetic testing through chorionic villus, amniotic fluid, or umbilical cord blood sampling during different gestation weeks as needed. The authors state that current carrier screening for DMD, which is provided for females with a family history of DMD, misses the many spontaneous cases resulting from unsuspected variants. Therefore, the authors suggest that “Carrier screening before or early in pregnancy will allow carrier females to receive genetic counseling and be informed of fertility choices and recurrent risk. Moreover, carrier screening will help carriers prepare for the possibility of manifesting DMD-related symptoms later on in life... Furthermore, female relatives of positive carriers should be recommended for genetic testing in order to evaluate their carrier status (Han et al., 2020).”

## **Facioscapulohumeral Muscular Dystrophy (FSHD)**

FSHD, an autosomal dominant genetic disorder, is caused by a deletion of the macrosatellite repeat regions D4Z4 of the *DUX4* gene in the subtelomeric region of chromosome 4q. In healthy individuals, the *DUX4* gene is epigenetically silenced in somatic tissues; however, contraction of the D4Z4 repeats allows for inefficient chromatin silencing due to abnormal chromatin structure, resulting in inappropriate somatic expression. Unaffected individuals have a variable number of D4Z4 repeats, ranging from 11 to more than 100, whereas FSHD1 patients have only 1 – 10 repeats on one of the copies of chromosome 4. The *DUX4* protein is usually only expressed in the germline as a DNA-binding protein with presumed transcription factor activity. Its toxicity in somatic cells is unknown. Two forms of FSHD have been classified—FSHD1, the major form due to a major contraction of the

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D4Z4 macrosatellite repeat sequences, and FSHD2, a minor form with a normal number of D4Z4 repeats but abnormal D4Z4 chromatin structure. FSHD2 patients have a disease status that cannot be confirmed by using the standard molecular diagnostic testing used in FSHD1 patients (van der Maarel, Tawil, & Tapscott, 2011). Further, 85% of patients with FSHD2 have mutations in the *SMCHD1* gene on chromosome 18, which encodes for a chromatin modifier believed to be involved in maintaining the D4Z4 chromatin structure (R. J. Lemmers et al., 2012)

FSHD patients exhibit a progressive muscular dystrophy with variability of affected muscles between patients. Generally, muscles of the face, arms, legs, shoulders, and abdomen can be affected. Serum-based diagnostic testing for FSHD has been elusive. A cross-sectional study by Petek and colleagues, using high-throughput proteomics, shows that the levels of creatine kinase MM and MB isoforms, carbonic anhydrase III, and troponin I type 2 were elevated at least 1.5-fold in affected individuals and correlated with the severity and state of disease (Petek et al., 2016). Because of the variability of FSHD, genetic testing is still “the preferred diagnostic choice” (Lemmers, O’Shea, Padberg, Lunt, & van der Maarel, 2012).

Methylation of the D4Z4 regions also plays a role in disease expression and progression (Haynes, Bomszyk, & Miller, 2018; Mul et al., 2018; van der Maarel et al., 2011). A study by Mul and colleagues researched the clinical variability of FSHD1 patients for a possible linkage between the severity of disease, the repeat array size of D4Z4, and D4Z4 methylation. Unsurprisingly, unaffected gene carriers had both a higher number of array repeats and higher methylation levels. One interesting result is that the location of the affected body region did show a correlation between disease severity and DNA modification. “The D4Z4 repeat array size and D4Z4 methylation contribute to variability in disease severity and penetrance, but other disease modifying factors must be involved as well. The larger effect of the D4Z4 repeat array on facial muscle involvement suggests that these muscles are more sensitive to the influence of the FSHD1 locus itself, whereas leg muscle involvement seems highly dependent on modifying factors (Mul et al., 2018).”

## **Clinical Validity and Utility of FSHD Genetic Testing**

The data on the clinical validity and utility of FSHD genetic testing is limited. The American Academy of Neurology and the American Association of Neuromuscular & Electrodiagnostic Medicine released joint guidelines stating the following: “our systematic review identified 9 Class III studies from specialty clinics that, together, demonstrate that the finding of a D4Z4 contraction on chromosome 4q35 likely has a sensitivity of 93% and a specificity of 98% for diagnosis of clinically defined FSHD (Tawil et al., 2015).” A 2010 study of more than 800 individuals, however, question the criteria for the molecular diagnosis of FSHD. In this study, 3% of asymptomatic, healthy individuals reported a reduced number of D4Z4 repeats, varying 4 to 8 units on chromosome 4; further, almost one-half of probands had a normal copy number of D4Z4 repeats. These “results suggest that the genetic basis of FSHD, which is remarkably heterogeneous, should be revisited because this has important implications for genetic counseling and prenatal diagnosis of at-risk families (Scionti et al., 2012).”

The most common method of molecular diagnosis for FSHD is pulsed-field gel electrophoresis with Southern Blotting to discriminate between chromosome 4 and chromosome 10 D4Z4 arrays. A study by Dai and colleagues describes a novel method to characterize the D4Z4 repeat numbers in FSHD by using a single molecule optical mapping platform that helps detect structural variants. With Bionano genome mapping, the number of D4Z4 repeats with 4qA allelic configuration and the levels of postzygotic mosaicism were determined. In the study, the primary cohort consisting of five patients had a confirmed positive diagnosis of FSHD based on Southern blot analysis. The second cohort consisted of eight patients that were suspected to have FSHD, but the patients did not have a prior molecular diagnosis. Optical mapping was performed, and Southern blot was used as a validation assay. In both cohorts, the results obtained from optical mapping have 100% concordance with the results from Southern blot analysis. Although optical mapping is a novel method that can improve accuracy and reliability of FSHD molecular testing, the authors also discuss the disadvantages of the

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optical mapping platform. Optical mapping is an expensive and time-consuming tool compared to Southern blot, which works reliably for diagnosing patients with 1-10 D4Z4 repeats in a cost-effective manner. Despite the disadvantages, the authors believe that costs for optical mapping will decrease and the tool will be incorporated into the clinical setting (Dai et al., 2020).

## Limb-Girdle Muscular Dystrophies

Generally, LGMDs are uncommon disorders with an estimated prevalence ranging from 0.07 per 100,000 to 0.43 per 100,000. The most common LGMD, which is BMD, has an estimated prevalence of 2.38–7.29 per 100,000 (Narayanaswami et al., 2014).

The LGMDs vary widely in their genetics and clinical features, ranging from mild forms allowing patients to maintain a fairly normal life to severe deterioration of proximal limb muscles with significant physical weakness and shortened life-span (Monies et al., 2016). Currently, thirty-one LGMD loci have been identified: “eight autosomal dominant and 23 autosomal recessive. The dominant forms (LGMD1) are: *LGMD1A* (myotilin), *LGMD1B* (lamin A/C), *LGMD1C* (caveolin 3), *LGMD1D* (DNAJB6), *LGMD1E* (desmin), *LGMD1F* (transportin 3), *LGMD1G* (HNRPDL), *LGMD1H* (chr. 3). The autosomal recessive forms (LGMD2) are: *LGMD2A* (calpain 3), *LGMD2B* (dysferlin), *LGMD2C* ( $\gamma$  sarcoglycan), *LGMD2D* ( $\alpha$  sarcoglycan), *LGMD2E* ( $\beta$  sarcoglycan), *LGMD2F* ( $\delta$  sarcoglycan), *LGMD2G* (telethonin), *LGMD2H* (TRIM32), *LGMD2I* (FKRP), *LGMD2J* (titin), *LGMD2K* (POMT1), *LGMD2L* (anoctamin 5), *LGMD2M* (fukutin), *LGMD2N* (POMT2), *LGMD2O* (POMTnG1), *LGMD2P* (dystroglycan), *LGMD2Q* (plectin), *LGMD2R* (desmin), *LGMD2S* (TRAPPC11), *LGMD2T* (GMPPB), *LGMD2U* (ISPD), *LGMD2V* (Glucosidase, alpha), *LGMD2W* (PINCH2) (Nigro & Savarese, 2014).”

## *Clinical Validity and Utility of LGMD Genetic Testing*

Based on published literature, the clinical validity of genetic testing for LGMD is difficult to ascertain. The yield of genetic testing in patients with signs and symptoms of LGMD varies depending on the mutation and population characteristics. Some studies conclude that the clinical validity is reasonably high (Fanin et al., 2009; Norwood, de Visser, Eymard, Lochmuller, & Bushby, 2007). According to Norwood et al. (2007), “DNA analysis directed to provide confirmation of mutation in the affected gene(s) is the gold standard of diagnosis, and necessary to be able to offer carrier or presymptomatic testing to other family members.” Other researchers have attempted to utilize whole-exome sequencing to diagnose LGMD in 100 individuals with familiar LGMD; however, a diagnostic success rate of only 45% was achieved (Ghaoui et al., 2015).

Monies et al. (2016) screened 50 random genetically unstudied families with LGMD via a gene panel incorporating 759 OMIM (Online Mendelian Inheritance in Man) genes associated with neurological disorders. OMIM is a catalogue of human genes and genetic disorders that provides comprehensive information based on the periodical biomedical literature (Amberger, Bocchini, Schiettecatte, Scott, & Hamosh, 2014). The panel “identified the mutation in 76 % of families (38/50; 11 novel). A total of 34 families had mutations in LGMD-related genes with four others having variants not typically associated with LGMD. The majority of cases had recessive inheritance with homoallelic pathogenic variants (97.4 %, 37/38), as expected considering the high rate of consanguinity in the study population.” The authors concluded that the “neurological panel achieved a high clinical sensitivity (76 %) and is an effective first-line laboratory test in patients with LGMD and other myopathies. This sensitive, cost-effective, and rapid assay significantly assists clinical practice especially in these phenotypically and genetically heterogeneous disorders. Moreover, the application of the American College of Medical Genetics (ACMG) and Association for Molecular Pathology (AMP) guidelines applied in the classification of variant pathogenicity provides a clear interpretation for physicians on the relevance of such findings (Monies et al., 2016).”

Harris et al. (2017) performed whole exome sequencing (WES) on 104 patients with LGMD in which standard gene testing had not yet yielded a diagnosis, and 91 patients using sequential gene by gene

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testing. They found that “patients selected for WES had undergone more extensive prior testing than those undergoing standard genetic testing, and on average had had eight genes screened already. In this extensively investigated cohort WES identified the genetic diagnosis in 28 families (28/75, 37%), including the identification of the novel gene *ZAK* and two unpublished genes. WES of a single affected individual with sporadic disease yielded a diagnosis in 13/38 (34%) of cases. In comparison, conventional gene by gene testing provided a genetic diagnosis in 28/84 (33%) families.” The authors concluded that “WES was able to overcome many limitations of standard testing and achieved a higher rate of diagnosis than standard testing even in this cohort of extensively investigated patients. Earlier application of WES is therefore likely to yield an even higher diagnostic rate. We obtained a high diagnosis rate in simplex cases and therefore such individuals should be included in exome or genome sequencing projects. Disease due to somatic mosaicism may be increasingly recognized due to the increased sensitivity of next generation sequencing techniques to detect low level mosaicism (Harris et al., 2017).” A similar study by Reddy and colleagues reported 40% of the LGMD families tested “had novel and previously reported pathogenic mutations, primarily in LGMD genes, and also in genes for Duchenne muscular dystrophy, facioscapulohumeral muscular dystrophy, congenital myopathy, myofibrillar myopathy, inclusion body myopathy and Pompe disease (Reddy et al., 2017).”

## Guidelines and Recommendations

### Best Practice Guidelines on Molecular Diagnostics in Duchenne/Becker Muscular Dystrophies Workshop Report (Abbs et al., 2010)

The international workshop comprised of scientists from Europe, the US, India, and Australia was organized and sponsored by the European Neuro-Muscular Centre, the European Molecular Genetics Quality Network, TREAT-NMD, and Euro-Gentest. The flow chart for the diagnostic work-up of a dystrophinopathy they recommend is shown below in Figure 1 (Abbs et al., 2010).

*S. Abbs et al./Neuromuscular Disorders 20 (2010) 422–427*

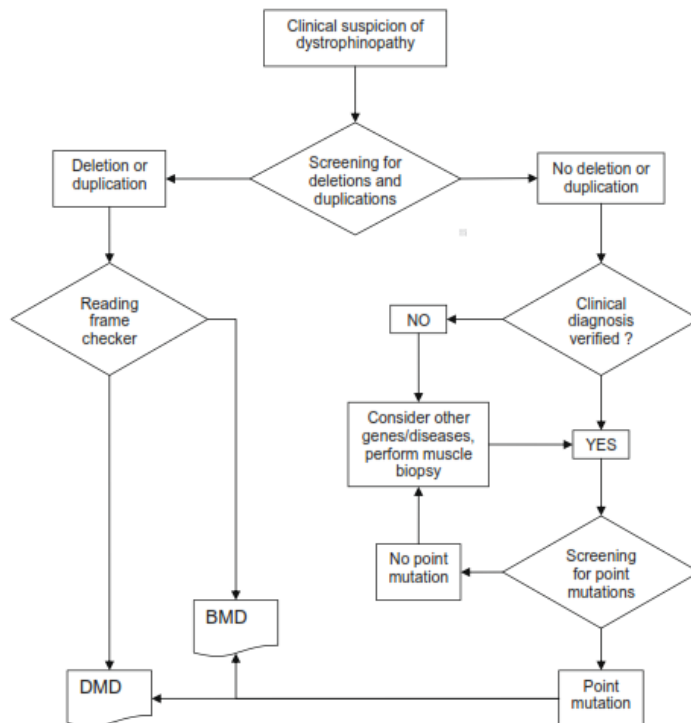


Fig. 1. Flow chart for the diagnostic work-up of a dystrophinopathy.



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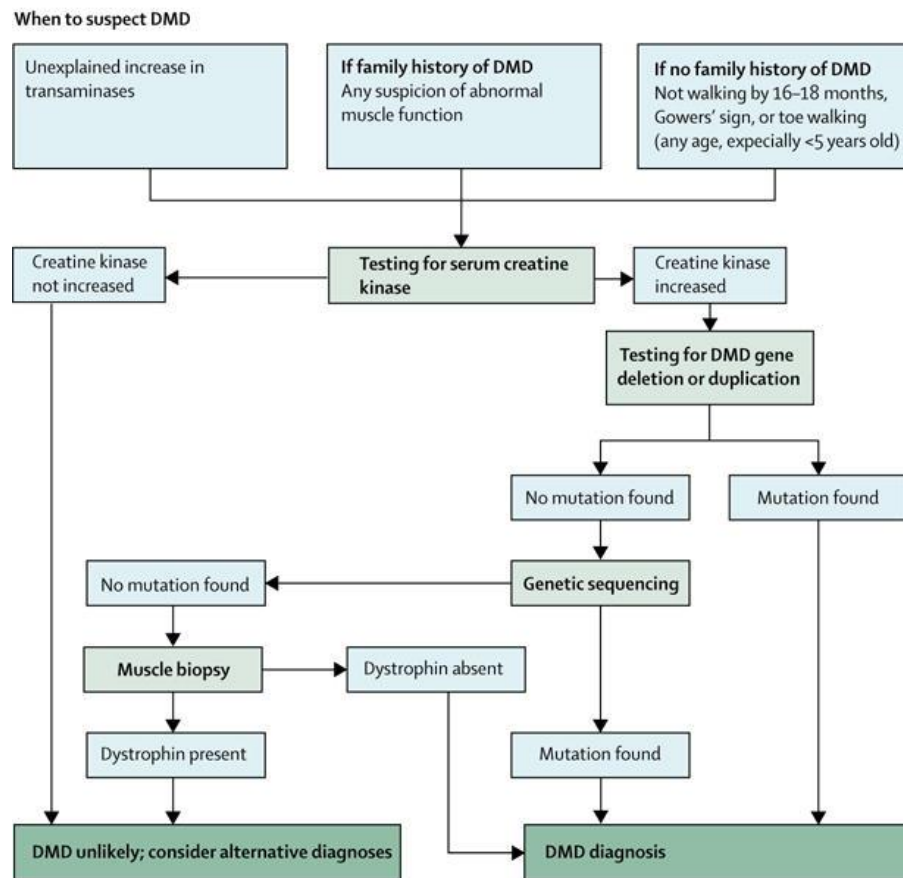
Recommendations for testing are: If there is a clinical suspicion of a dystrophinopathy, first screen for deletions and duplications. If no deletion or duplication is detected, but the clinical diagnosis is verified, screening for point mutations should be performed (Abbs et al., 2010).

The DMD Care Considerations Working Group (Bushby et al., 2010(**Birnkrant et al., 2018; Bushby et al., 2010**))

The CDC selected 84 clinicians to comprise the DMD Care Considerations Working Group to develop recommendations regarding all aspects of DMD care, including the diagnosis and genetic testing of muscular dystrophy. They state the following: “Testing for a DMD mutation in a blood sample is always necessary even if DMD is first confirmed by the absence of dystrophin protein expression on muscle biopsy. The results of genetic testing provide the clinical information required for genetic counselling, prenatal diagnosis, and consideration for future mutation-specific therapies... If analysis by one or more of these techniques leads to the identification and full characterisation of a dystrophin mutation, then no further testing is required. If deletion/ duplication testing is negative, then dystrophin gene sequencing should be done to look for point mutations or small deletions/insertions. Full characterisation of the mutation (deletion endpoints or exact position of any point mutation) is required to allow correlation of the predicted effect of the mutation on the reading frame of the gene, which is the major determinant of the phenotypic variability seen in dystrophinopathy, as well as to determine eligibility for the mutation-specific treatments currently in trials (Bushby et al., 2010).”

More recently, an update of the 2010 DMD Care considerations was published to further improve patient care. A diagnostic flow chart for DMD was provided and can be found below (Birnkrant et al., 2018).

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## Most commonly observed early signs and symptoms in patients with DMD

### Motor

- Abnormal gait
- Calf pseudohypertrophy
- Inability to jump
- Decreased endurance
- Decreased head control when pulled to sit
- Difficulty climbing stairs
- Flat feet
- Frequent falling or clumsiness
- Gowers' sign on rising from 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

### Non-motor

- Behavioural issues
- Cognitive delay
- Failure to thrive or poor weight gain
- Learning and attentional issues
- Speech delay or articulation difficulties

The DMD Care Considerations Working Group has stated that “Because approximately 70% of individuals with DMD have a single-exon or multi-exon deletion or duplication in the dystrophin gene, dystrophin gene deletion and duplication testing is usually the first confirmatory test. Testing is best done by multiplex ligation-dependent probe amplification (MLPA) or comparative genomic hybridisation array, since use of multiplex PCR can only identify deletions... If deletion or duplication testing is negative, genetic sequencing should be done to screen for the remaining types of mutations that are attributed to DMD (approximately 25–30%)... Finally, if genetic testing does not confirm a clinical diagnosis of DMD, then a muscle biopsy sample should be tested for the presence of

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dystrophin protein by immunohistochemistry of tissue cryosections or by western blot of a muscle protein extract (Birnkrant et al., 2018).” Also stated is that “Family members of an individual with DMD should receive genetic counselling to establish who is at risk of being a carrier. Carrier testing is recommended for female relatives of a boy or man who has been genetically confirmed to have DMD (Birnkrant et al., 2018).”

**American Academy of Neurology (AAN) and the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) (P. B. Kang et al., 2015; Narayanaswami et al., 2014) (reaffirmed in 2018 (Peter B. Kang et al., 2018))**

The Guideline Development Subcommittee of the American Academy of Neurology and the Practice Issues Review Panel of the American Association of Neuromuscular and Electrodiagnostic Medicine published recommendations that “Targeted genetic testing often identifies causative mutations in the classic CMD subtypes... Genetic diagnoses are beneficial to the patient, as they often enable physicians to provide more accurate prognoses and facilitate genetic counseling and family-planning discussions, and may enable patients to become more aware of future clinical trials for which they may be eligible... when available and feasible, physicians might order targeted genetic testing for specific CMD subtypes that have well-characterized molecular causes” and “In individuals with CMD who either do not have a mutation identified in one of the commonly associated genes or have a phenotype whose genetic origins have not been well characterized, physicians might order whole-exome or whole-genome sequencing when those technologies become more accessible and affordable for routine clinical use (P. B. Kang et al., 2015).”

In 2014, the American Academy of Neurology and the Practices Issues Review Panel of the American Association of Neuromuscular and Electrodiagnostic Medicine issued evidenced-based guidelines for the diagnosis and treatment of limb-girdle and distal dystrophies, who made the following recommendations (Narayanaswami et al., 2014):

For the diagnosis of LGMD:

- For patients with suspected muscular dystrophy, clinicians should use a clinical approach to guide genetic diagnosis based on the clinical phenotype, including the pattern of muscle involvement, inheritance pattern, age at onset and associated manifestations (e.g., early contractures, cardiac or respiratory involvement) (Level B recommendation).
- In patients with suspected muscular dystrophy in whom initial clinically directed genetic testing does not provide a diagnosis, clinicians may obtain genetic consultation or perform parallel sequencing of targeted exomes, whole-exome sequencing, whole genome screening, or next-generation sequencing to identify the genetic abnormality (Level C recommendation).

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

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immunosuppressants make a strong case for establishing a genetic diagnosis, which often provides patients a sense of closure. Establishing a genetic diagnosis is crucial for genetic counseling to inform decision-making about having children and for screening of offspring. Treatment of cardiomyopathy, arrhythmias, and ventilatory failure prolongs life and improves quality of life in patients with other neuromuscular diseases (Narayanawami et al., 2014).”

## **American Academy of Neurology (AAN) (Tawil et al., 2015) (reaffirmed in 2018 (AAN, 2018))**

The American Academy of Neurology published evidence-based guidelines which found that “the finding of a D4Z4 contraction on chromosome 4q35 likely has a sensitivity of 93% and a specificity of 98% for diagnosis of clinically defined FSHD.” They recommend that “Clinicians should obtain genetic confirmation of FSHD1 in patients with atypical presentations and no first-degree relatives with genetic confirmation of the disease [Level B].” Concerning the use of genetics as a predictor of severity in FSHD, they recommend, “Large D4Z4 deletion sizes (contracted D4Z4 allele of 10–20 kb) should alert the clinician that the patient is more likely to develop more significant disability and at an earlier age. Patients with large deletions are also more likely to develop symptomatic extramuscular manifestations [Level B] (Tawil et al., 2015).”

## **International Standard of Care Committee for Congenital Muscular Dystrophy (C. H. Wang et al., 2010)**

As a part of the guidelines concerning newly diagnosed patients, they recommend, “if a genetic diagnosis is known, the recurrence risk and impact on future family planning should be discussed. Even if the exact genetic defect is not known, recurrence risk can sometimes be discussed using a common genetic model that is often associated with the diagnosis (C. H. Wang et al., 2010).”

## **171st European Neuromuscular Centre International Workshop on Standards of Care and Management of Facioscapulohumeral Muscular Dystrophy (FSHD) (R. J. L. F. Lemmers et al., 2012)**

In a report from the 171st European Neuromuscular Centre International Workshop Standards of Care and Management of FSHD held in January 2010, it is stated that “when a physician concludes facioscapulohumeral syndrome based on clinical findings, the odds are in favor of FSHD, and genetic testing is the preferred diagnostic choice (R. J. L. F. Lemmers et al., 2012).”

## **Evidence-Based Consensus and Systematic Review on Reducing the Time to Diagnosis of Duchenne Muscular Dystrophy Joint Report of the EPNS, MDA, PPMD, TREAT-NMD, and DPPI (Aartsma-Rus et al., 2019)**

According to this evidence-based report endorsed by the European Paediatric Neurology Society (EPNS), the Muscular Dystrophy Association (MDA), Duchenne Parent Project Italy (DPPI), Parent Project Muscular Dystrophy (PPMD), and TREAT-NMD, “Genetic testing is crucial for obtaining a complete diagnosis of DMD, and should be considered the gold standard” (Aartsma-Rus et al., 2019); accepted DMD symptoms are listed and include “calf hypertrophy (pseudohypertrophy); delayed walking; difficulty climbing/descending stairs; difficulty rising from the floor; difficulty running/walking; elevated serum CK levels (including elevated ALT and AST); a family history of DMD; frequent falls; Gowers' sign; male sex; and muscle weakness;” additional recommendations include that “patients with signs and symptoms of DMD and elevated serum CK levels should be referred for genetic testing to either a clinical geneticist or a neuromuscular specialist” (Aartsma-Rus et al., 2019). In regards to other family members, Aartsma-Rus et al. (2019) recommends that “After a patient receives a complete genetic diagnosis of DMD, it is mandatory that carrier testing of the mother and other at-risk female family members be offered with appropriate pre- and postgenetic counseling.”

## **U.S. Preventive Services Task Force (USPSTF) Recommendations**

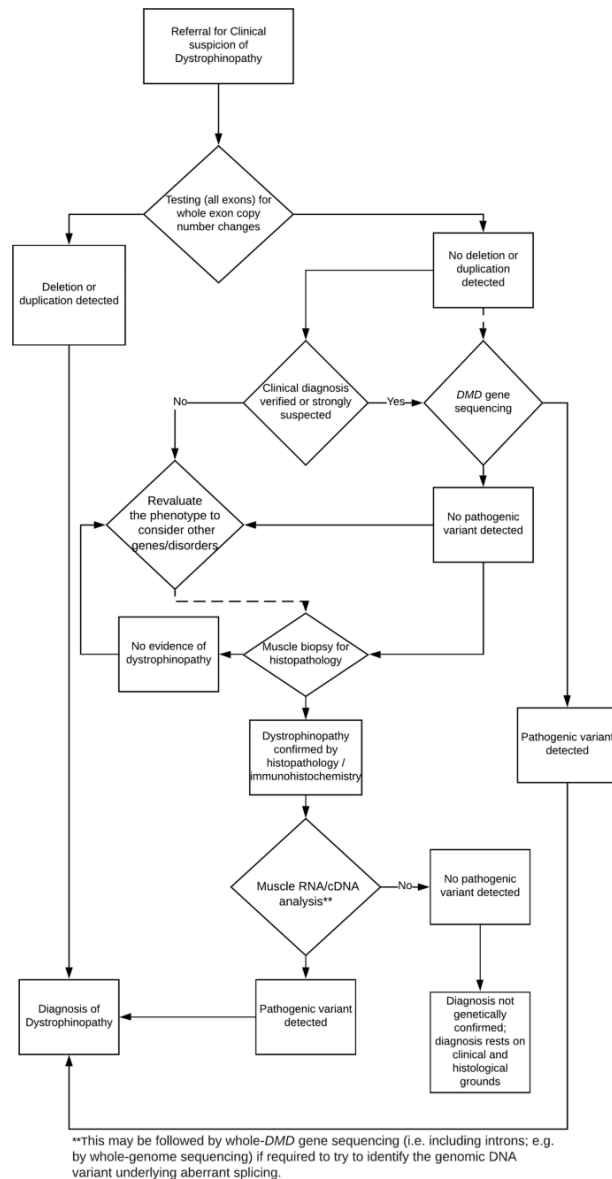
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No U.S. Preventive Services Task Force recommendations for genetic testing for muscular dystrophy have been identified. A search for “muscular dystrophy” on the USPSTF website turned up 0 results on October 2<sup>nd</sup>, 2020.

## **European Molecular Genetics Quality Network (EMQN) Best Practice Guidelines on molecular diagnostics in the Duchenne/Becker muscular dystrophies (Fratter et al., 2020)**

The EMQN summarizes current diagnostic methods to analyze the *DMD* gene and categorizes these methods according to specificity of the tests into Level 1 (copy number variations detection), Level 2 (small variants detection), and Level 3 (RNA Analysis). 78% of the pathogenic *DMD* variants is due to whole-exon deletions and duplications; therefore, detection of the relative copy number of all exons within the *DMD* gene (copy number variations) is the first level of diagnostic tests offered. Several quantitative tests can be used to detect these copy number variations (CNVs). The most reliable method is multi-plex ligation-dependent probe amplification (MLPA), which detects the number of deletions or duplications to the exon level. MLPA is more reliable when there are multiple exons involved, but less if there is a single exon deletion. Therefore, real-time PCR, multi-plex PCR, Sanger sequencing, or microsatellite marker analysis must follow to confirm single exon deletions. Comparative genomic hybridization (CGH) is another method which provides a slightly higher detection rate than MLPA by use of oligonucleotide probes to interrogate copy number across the entire 2.2 Mb genomic region of the *DMD* gene. The last method is next generation sequencing (NGS), which can detect single nucleotide variants (SNVs) and copy number variations (CNVs); however, NGS is not routinely used to detect CNVs because it is not sensitive enough to pick up on all types of CNVs. Level 2 testing detects missense, nonsense, small insertions and deletions, and indel and splicing variants through either Sanger sequencing or NGS. NGS is less time consuming as it allows for many targets to be sequenced with deep sequence coverage in multiple patients at a time and enhances detection of low-level somatic mosaicism in patients’ or probands’ mothers; however, Sanger sequencing is still the standard method used for known familial variant testing. Level 3 testing, such as muscle cDNA analysis, is used when a patient presents with clinical symptoms of a dystrophinopathy, but no CNVs or small variants were detected from Level 1 and Level 2 diagnostic techniques.

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A flowchart for the recommended molecular diagnostic algorithm for dystrophinopathy is shown in the figure above (Fratter et al., 2020). When dystrophinopathy is suspected due to clinical symptoms, high serum creatine kinase levels, and a possible family history, molecular testing to detect copy number variations (CNVs) is recommended. If a pathogenic deletion and duplication is not detected, the next step is to sequence the coding region of the entire *DMD* gene. If a pathogenic variant is not detected from these two tests, a muscle biopsy, dystrophin gene analysis via immunohistochemistry, or muscle cDNA sequencing may be performed. If the patient presents with a positive muscle biopsy test and positive symptoms of a dystrophinopathy, but no pathogenic variant is detected through genetic testing, the patient should still be diagnosed with a dystrophinopathy (Fratter et al., 2020).

The EMQN also provides guidelines on genetic testing for females affected by dystrophinopathies. Although dystrophinopathies predominantly affect males, females could have a pathogenic *DMD* variant and present with a milder phenotype most likely due to a skewed X-inactivation. In this case, the diagnostic method would be identical to the one presented in the flowchart: evaluation of clinical symptoms, CNV analysis and *DMD* gene sequencing followed by muscle biopsy, dystrophin gene analysis, and muscle cDNA sequencing as needed. If a female presents with the complete *DMD*

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phenotype, karyotyping is recommended due to possible chromosomal aberrations or autosomal translocations that could cause 100% skewed X-inactivation.

Females who are carriers of dystrophinopathies are usually clinically asymptomatic but may develop some symptoms during their lifetime or pass it down to their children. Therefore, carrier testing is important for family planning. If the familial pathogenic variant is known, then two complementary tests should be performed (MLPA and Sanger Sequencing or MLPA and microsatellite analysis). High density array CGH can also be used, which is a single test that interrogates multiple loci within the deletion or duplication. If the familial pathogenic variant is not known and an affected male in the family is not available, then female carriers who are at risk of being carriers should be offered CNV analysis and *DMD* gene sequencing followed by muscle biopsy, dystrophin gene analysis, and muscle cDNA sequencing as needed. Measuring serum creatine kinase levels may also be helpful (Fratter et al., 2020).

EMQN also comments on prenatal diagnosis of dystrophinopathies. Since it is not possible to predict whether a female will present symptoms of a dystrophinopathy, prenatal diagnosis should only be performed on pregnancies with a male fetus unless there is documented familial reoccurrence of complete skewed X inactivation. Prenatal testing is performed on placental biopsy through chorionic villus sampling (CVS) within 11-12 weeks of gestation or amniocentesis within 15-17 weeks of gestation. CVS is the preferred method as it provides higher DNA quality and greater safety for the pregnancy. The obtained DNA from placental biopsy can be analyzed through next genome sequencing (NGS) or CNV detection. For non-invasive prenatal diagnostic options, relative haplotype dosage analysis (RHDO) may be performed. “RHDO analysis examines SNPs in the cell-free DNA from a maternal blood sample and shows whether the male fetus has inherited the high risk or low risk haplotype across the *DMD* gene (Fratter et al., 2020).”

## Applicable Federal Regulations

A search of the FDA Device database on 10/02/2020 for “genotyping tests” yielded 15 results. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

## Billing/Coding/Physician Documentation Information

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: 81161, 81400, 81404, 81405, 81406, 81408, 81479, 0218U.*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## Scientific Background and Reference Sources

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Specialty Matched Consultant Advisory Panel review 7/2020.

Medical Director review 7/2020.

## Policy Implementation/Update Information

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1/1/2019 New policy developed. BCBSNC will provide coverage for genetic testing for facioscapulohumeral muscular dystrophy when it is determined to be medically necessary because criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)

### **For policy titled: Genetic Testing for Duchenne Becker, Facioscapulohumeral, Limb-Girdle Muscular Dystrophies**

4/16/2019 The following policies have been combined to create a single policy concerning the genetic testing for muscular dystrophies: Genetic Testing for Duchenne and Becker Muscular Dystrophy, Genetic Testing for Facioscapulohumeral Muscular Dystrophies AHS – M2076, Mutation Testing for Limb-Girdle Muscular Dystrophies AHS – M2128. These 3 separate policies are archived. Description section, policy guidelines sections updated with language and criteria indications to reflect the combined policies. When Covered and When Not Covered sections revised to include criteria indications from the three original policies; no change to policy intent. Billing/Coding section and referenced updated. Medical Director review 4/2019. (jd)

10/29/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (hb)

2/11/20 Annual review by Avalon 4<sup>th</sup> Quarter 2019 CAB. No revisions and no change to policy intent. Medical Director review 12/2019. (jd)

7/28/20 Specialty Matched Consultant Advisory Panel review 7/2020. Medical Director review 7/2020. (jd)

10/1/20 The following code was added to the Billing/Coding section effective 10/1/20: 0218U. (jd)

2/9/21 Annual review by Avalon 4<sup>th</sup> Quarter 2020 CAB. Added “Related Policies” to the Description section. Minor revision to When Covered section item #1-a.: changed “In a male” to

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“Individuals”. Minor revisions to policy guidelines and references. No change to policy intent.  
Medical Director review 1/2021. (jd)

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