



# Genetic Testing for Duchenne and Becker Muscular Dystrophy

Policy # 00471

Original Effective Date: 07/15/2015

Current Effective Date: 08/14/2023

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

## When Services Are Eligible for Coverage

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider genetic testing for Duchenne muscular dystrophy (DMD) gene variants to be **eligible for coverage**.\*\*

### Patient Selection Criteria

Coverage eligibility for genetic testing for DMD gene variants will be considered when **ANY** the following criteria are met:

- In a male with signs and symptoms of a dystrophinopathy in order to confirm the diagnosis and direct treatment; **OR**
- For at-risk female relatives (see Policy Guidelines section):
  - To confirm or exclude the need for cardiac surveillance;
  - For preconception testing to determine the likelihood of an affected offspring in a woman considering a pregnancy; **OR**
- For at-risk male offspring (see Policy Guidelines section):
  - To confirm or exclude the need for medical and cardiac surveillance.

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### When Services Are Considered Investigational

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers the use of genetic testing for Duchenne muscular dystrophy (DMD) gene variants when patient selection criteria are not met to be **investigational**.\*

Based on review of available data, the Company considers genetic testing for Duchenne muscular dystrophy (DMD) gene variants in all other situations to be **investigational**.\*

### Policy Guidelines

#### **DMD gene testing**

Females heterozygous for a Duchenne muscular dystrophy (DMD) disease-associated variant are at increased risk for cardiomyopathy and need routine cardiac surveillance and treatment.

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.

An at-risk male is defined as an asymptomatic male offspring of a female carrier or an asymptomatic male sibling of an individual with a DMD-associated dystrophinopathy.

#### **Genetic Counseling**

Experts recommend formal genetic counseling for individuals who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some individuals; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

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### **Background/Overview**

#### **Dystrophinopathies**

The dystrophinopathies include a spectrum of muscle diseases. The mild end of the spectrum includes asymptomatic increases in serum concentration of creatine phosphokinase and clinical symptoms such as muscle cramps with myoglobinuria and/or isolated quadriceps myopathy. The severe end of the spectrum includes progressive muscle diseases that lead to substantial morbidity and mortality. When skeletal muscle is primarily affected, the disease is classified as Duchenne muscular dystrophy (DMD) or Becker muscular dystrophy (BMD); when the heart is primarily affected, the disease is classified as DMD-associated dilated cardiomyopathy (left ventricular dilation and heart failure).

#### **Duchenne Muscular Dystrophy**

DMD, the most common muscular dystrophy, is a severe childhood X-linked recessive disorder that results in significant disability due to skeletal myopathy and cardiomyopathy. The disease is characterized by progressive, symmetric muscle weakness and gait disturbance resulting from a defective dystrophin gene. According to a 2022 systematic review and meta-analysis, the global prevalence of DMD is estimated at 4.8 cases (95% confidence interval [CI], 3.6 to 6.3) per 100,000 people. Approximately one-third of DMD cases arise from de novo variants and have no known family history. Infant males with DMD are often asymptomatic. Manifestations may be present as early as the first year of life in some individuals, but clinical manifestations most often appear during preschool, from years 2 to 5. Affected children present with gait problems, calf hypertrophy, positive Gower sign, and difficulty climbing stairs. The affected child's motor status may plateau between 3 and 6 years of life with deterioration beginning at 6 to 8 years. Most individuals will be wheelchair-bound by ages 9 to 12 years but will retain preserved upper-limb function until a later period. Cardiomyopathy occurs after 18 years of age. Late complications are cardiorespiratory (eg, decreased pulmonary function as a result of respiratory muscle weakness and cardiomyopathy). These severe complications commonly appear in the second decade of life and eventually lead to death. Few individuals with DMD survive beyond the third decade.

#### **Becker Muscular Dystrophy**

BMD is characterized by later onset skeletal muscle weakness. Individuals remain ambulatory into their 20s. Despite the milder skeletal muscle involvement, heart failure from cardiomyopathy is a common cause of morbidity and the most common cause of death in these individuals, with a mean

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age of death in the mid-40s. According to a 2022 systematic review and meta-analysis, the global prevalence of BMD is estimated at 1.6 cases (95% CI, 1.1 to 2.4) per 100,000 people.

### Female Carriers

Females heterozygous for a *DMD* disease-associated variant can manifest symptoms of the disease. An estimated 2.5% to 7.8% of female carriers are manifesting carriers who develop symptoms ranging from mild muscle weakness to a rapidly progressive DMD-like muscular dystrophy. Female carriers are at increased risk for dilated cardiomyopathy. Most heterozygous women do not show severe myopathic features of DMD, possibly due to compensation by a normal X chromosome with inactivation of the mutated *DMD* gene in the affected X chromosome. In some cases, this compensation can be reversed by a nonrandom or skewed inactivation of the X chromosome, resulting in greater expression of the affected X chromosome and some degree of myopathic features. Other mechanisms of manifesting female carriers include X chromosome rearrangement involving the *DMD* gene and complete or partial absence of the X chromosome (Turner syndrome).

### Clinical Diagnosis

#### Duchenne Muscular Dystrophy

Suspicion of DMD should be considered irrespective of family history; it is most commonly triggered by the observation of abnormal muscle function in a male child, the detection of an increase in serum creatine kinase tested for unrelated indications, or detection of increased serum transaminases (aspartate aminotransferase and alanine aminotransferases). Clinical examination by a neuromuscular specialist for DMD includes visual inspection of mechanical function such as running, jumping, climbing stairs, and getting up from the floor. Common presenting symptoms include abnormal gait with frequent falls, difficulties rising from the floor or tip-toe walking, and pseudohypertrophy of the calves. A clinical examination may reveal decreased or lost muscle reflexes and, commonly, a positive Gower sign. An elevation of serum creatine kinase, at least 10 to 20 times normal levels (between 5000 IU/L and 150000 IU/L), is nonspecific to DMD but is always present in affected individuals. Electromyography and nerve conduction studies were traditional parts of the assessment of neuromuscular disorders, but these tests may not be necessary for assessment of DMD. An open skeletal muscle biopsy is needed when a test for deletions or duplications of the *DMD* gene is negative. The biopsy will provide general signs of muscular dystrophy, including muscle fiber degeneration, muscle regeneration, and increased content of

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## Genetic Testing for Duchenne and Becker Muscular Dystrophy

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connective tissue and fat. Dystrophin analysis of a muscle biopsy will always be abnormal in affected individuals but is not specific to DMD.

### **Becker Muscular Dystrophy**

BMD is clinically similar to DMD but is milder and has a later onset. BMD presents with progressive symmetric muscle weakness, often with calf hypertrophy, although the weakness of quadriceps femoris may be the only sign. Activity-induced cramping may be present in some individuals, and flexion contractures of the elbows may be present late in the course. Neck flexor muscle strength is preserved, which differentiates BMD from DMD. Serum creatine kinase shows moderate-to-severe elevation (5 to 100 times the normal level).

### **Molecular Diagnosis**

*DMD* is the only gene of which variants are known to cause DMD, BMD, and *DMD*-associated cardiomyopathy. Molecular genetic testing of *DMD* can establish the diagnosis of a dystrophinopathy without muscle biopsy in most individuals with DMD and BMD.

The dystrophinopathies are X-linked recessive and penetrance is complete in males. The gene that codes for dystrophin is the largest known human gene. A molecular confirmation of DMD and BMD is achieved by confirming the presence of a pathogenic variant in this gene by a number of available assays. The large size of the dystrophin gene results in a complex variant spectrum with over 5000 reported disease-associated variants, as well as a high spontaneous de novo variant rate.

### **Treatment**

There is no cure for DMD or BMD. Treatment is aimed at controlling symptoms to improve quality of life. However, the natural history of the disease can be changed by strategies such as corticosteroid therapy, proper nutrition, or rehabilitative interventions. Glucocorticoids were shown in a 1991 randomized controlled trial (RCT) to prolong the period of independent ambulation by 3 years. The goal of this therapy is to preserve ambulation and minimize later respiratory, cardiac, and orthopedic complications. Glucocorticoids work by decreasing inflammation, preventing fibrosis, improving muscle regeneration, improving mitochondrial function, decreasing oxidative radicals, and stopping abnormal apoptosis pathways. Bone density measurement and immunization are prerequisites for corticosteroid therapy initiation, which typically begins at 2 to 5 years of age, although there has been no demonstrated benefit of therapy before 5 years of age.

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Policy # 00471

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New therapeutic trials require accurate diagnoses of these disorders, especially when the therapy is targeted at specific pathogenic variants. Exon-skipping is a molecular therapy aimed at skipping the transcription of a targeted exon to restore a correct reading frame using antisense oligonucleotides. Exon-skipping may result in a DMD protein without the mutated exon and a normal, nonshifted reading frame. Exon-skipping may also restore DMD protein function so that the treated individual's phenotypic expression more closely resembles BMD. Several therapies are currently in clinical trials. Exon-skipping therapies using antisense oligonucleotides approved by the U.S. Food and Drug Administration include: eteplirsen (Exondys 51) for treatment for individuals who have a confirmed variant of the dystrophin gene amenable to exon 51 skipping, golodirsen (Vyondys 53), and viltolarsen (Viltepso) for individuals who have a confirmed mutation of the *DMD* gene that is amenable to exon 53 skipping. These approvals were based on improvements in the surrogate outcome of increased dystrophin production in skeletal muscle and benefits in clinical outcomes have not yet been established.

## **FDA or Other Governmental Regulatory Approval**

### **U.S. Food and Drug Administration (FDA)**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

## **Rationale/Source**

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

### **Description**

Variants in the Duchenne muscular dystrophy (*DMD*) gene, which encodes the protein dystrophin, may result in a spectrum of X-linked muscle diseases, including the progressive diseases Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) and dilated cardiomyopathy.

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## Genetic Testing for Duchenne and Becker Muscular Dystrophy

Policy # 00471

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Genetic testing can confirm a diagnosis of a dystrophinopathy and distinguish the less from more severe forms, as well as identify female carriers at risk.

### Summary of Evidence

For individuals who are male and have signs and symptoms of a dystrophinopathy who receive genetic testing for Duchenne muscular dystrophy (*DMD*) gene variants to confirm diagnosis without biopsy, the evidence includes case series and database entries describing screening and results of types of variants found in individuals with clinical signs of *DMD* or Becker muscular dystrophy (*BMD*). Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, quality of life, medication use, and resource utilization. Virtually all males with *DMD* or *BMD* have identifiable *DMD* disease-associated variants, indicating a high clinical sensitivity for genetic testing. The clinical utility of *DMD* gene testing can be established for the index case to confirm the diagnosis without a muscle biopsy, to initiate effective treatment, and to distinguish between *DMD* and the less severe *BMD*. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are female and are a relative of an individual with a *DMD*-associated dystrophinopathy who receive targeted *DMD* testing for a known familial variant to determine carrier status, the evidence includes case series and database entries describing screening and results of types of variants found in individuals with clinical signs of *DMD* or *BMD*. Relevant outcomes are test accuracy and validity, changes in reproductive decision making, symptoms, change in disease status, morbid events, quality of life, medication use, and resource utilization. Published data for the clinical validity for testing for a known familial variant are lacking but validity is expected to be high. Direct evidence on the clinical utility of *DMD* gene testing in at-risk female relatives is lacking. However, the chain of evidence is strong, because determination of carrier status in a female for a *DMD* familial variant necessitates or eliminates the need for routine cardiac surveillance and can indicate the likelihood of an affected offspring in women considering children. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic male offspring of a female *DMD* familial variant carrier or an asymptomatic male sibling of an individual with a *DMD*-associated dystrophinopathy who receive targeted *DMD* testing for a known familial variant to determine *DMD* status, the evidence includes case series and database entries. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, quality of life, medication use, and resource

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## Genetic Testing for Duchenne and Becker Muscular Dystrophy

Policy # 00471

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Current Effective Date: 08/14/2023

utilization. Published data for clinical validity of testing for a known familial variant are lacking, but validity is expected to be high. Direct evidence on the clinical utility of *DMD* gene testing in asymptomatic male offspring of a female *DMD* familial variant carrier or male sibling of an individual with a *DMD*-associated dystrophinopathy is also lacking. However, the chain of evidence is strong, because detection of the *DMD* familial variant necessitates or eliminates the need for increased medical surveillance or cardiac surveillance in an asymptomatic male offspring of a female carrier or the asymptomatic male sibling of an individual with a *DMD*-associated dystrophinopathy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

### **Supplemental Information**

#### **Practice Guidelines and Position Statements**

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

#### **Duchenne muscular dystrophy Care Considerations Working Group**

In 2010, an international working group comprised of 84 clinicians and scientists from government agencies, including the US Centers for Disease Control and Prevention, and advocacy organizations provided recommendations for providing coordinated multidisciplinary care in the diagnosis and treatment of Duchenne muscular dystrophy (DMD). Per the working group, genetic testing should first be used to screen for deletions and duplications. If no deletion or duplication is detected, screening for single nucleotide variants should be performed. For individuals diagnosed by genetic testing, muscle biopsy is optional to distinguish DMD from milder phenotypes.

In 2018, the DMD Care Considerations Working Group updated its Care Considerations recommendations. Their recommendations for genetic testing utilization in DMD diagnosis remained similar to their 2010 recommendations, with a recommendation to first screen for deletions and duplications, followed by genetic sequencing if no deletion or duplication is detected. A muscle biopsy is only recommended if genetic testing does not confirm a clinical diagnosis and DMD is still considered likely. The working group also recommended genetic counseling to family members of

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## Genetic Testing for Duchenne and Becker Muscular Dystrophy

Policy # 00471

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Current Effective Date: 08/14/2023

an individual with DMD to establish who is at risk of being a carrier. Carrier testing is recommended for female relatives of a male who has been genetically confirmed to have DMD.

### **The European Molecular Genetics Quality Network and EuroGenTest**

In 2010, a meeting of 29 senior scientists from the United States, Europe, India, and Australia established consensus best practice guidelines for the molecular diagnosis of Duchenne and Becker muscular dystrophy. Recommendations for testing were: 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, screen for single nucleotide variants.

In 2020, the best practice guidelines were updated to summarize current recommended technologies and methodologies in DMD gene analysis. The guideline's recommendations for testing are similar to 2010 recommendations. In terms of an initial screen, a diagnostic test that detects whole-exon deletions or duplications should be offered to detect copy number variations. Use of RNA-based analysis is recommended in individuals with a clinical diagnosis of dystrophinopathy but no copy number variations or small variants that were identified.

### **U.S. Preventive Services Task Force Recommendations**

Not applicable.

### **Medicare National Coverage**

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

### **Ongoing and Unpublished Clinical Trials**

A search of [ClinicalTrials.gov](https://clinicaltrials.gov) in January 2023 did not identify any ongoing or unpublished trials that would likely influence this review.

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## Genetic Testing for Duchenne and Becker Muscular Dystrophy

Policy # 00471

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Current Effective Date: 08/14/2023

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## Genetic Testing for Duchenne and Becker Muscular Dystrophy

Policy # 00471

Original Effective Date: 07/15/2015

Current Effective Date: 08/14/2023

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## **Policy History**

Original Effective Date: 07/15/2015

Current Effective Date: 08/14/2023

06/25/2015	Medical Policy Committee review
07/15/2015	Medical Policy Implementation Committee approval. New Policy.
06/30/2016	Medical Policy Committee review
07/20/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis codes
07/06/2017	Medical Policy Committee review
07/19/2017	Medical Policy Implementation Committee approval. The coverage statement was updated to add a third indication for male offspring of female carriers and male sibling of affected male. "Mutations" was changed to "variants" in the policy statements in keeping with updated genetics nomenclature. A new definition for "at-risk males" Note was added in the coverage section.
07/05/2018	Medical Policy Committee review
07/11/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2019	Coding update

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Policy # 00471

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Current Effective Date: 08/14/2023

07/03/2019	Medical Policy Committee review
07/18/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/02/2020	Medical Policy Committee review
07/08/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/16/2020	Coding update
07/01/2021	Medical Policy Committee review
07/14/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/07/2022	Medical Policy Committee review
07/13/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/06/2023	Medical Policy Committee review
07/12/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 07/2024

### **Coding**

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## Genetic Testing for Duchenne and Becker Muscular Dystrophy

Policy # 00471

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Current Effective Date: 08/14/2023

*contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.*

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0218U, 81161, 81408
HCPCS	No codes
ICD-10 Diagnosis	All related Diagnoses

\*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
  1. Consultation with technology evaluation center(s);
  2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
  3. Reference to federal regulations.

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## Genetic Testing for Duchenne and Becker Muscular Dystrophy

Policy # 00471

Original Effective Date: 07/15/2015

Current Effective Date: 08/14/2023

**\*\*Medically Necessary** (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

**NOTICE:** If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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