Genetic Testing for Dilated Cardiomyopathy

Policy # 00409
Original Effective Date: 03/19/2014
Current Effective Date: 07/10/2023

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.

Note: Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy is addressed separately in medical policy 00270.

Note: Genetic Testing for Cardiac Ion Channnelopathies is addressed separately in medical policy 00408.

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 comprehensive genetic testing for individuals with signs or symptoms of dilated cardiomyopathy which is considered idiopathic after a negative workup for secondary causes to be **eligible for coverage**** (See Policy Guidelines).

Based on review of available data, the Company may consider targeted genetic testing for asymptomatic individuals with a first-degree relative who has dilated cardiomyopathy and a known familial variant to be **eligible for coverage.****

Note:
If there is an evidence that previous genetic testing for dilated cardiomyopathy was completed, repeated testing is not necessary and is not eligible for coverage.

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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 genetic testing for dilated cardiomyopathy in all other situations to be **investigational.***

Policy Guidelines

Standard Workup for Patients With Signs or Symptoms of Dilated Cardiomyopathy

The standard workup for patients with signs or symptoms of dilated cardiomyopathy (DCM) includes a clinical exam, blood pressure monitoring, electrocardiography, echocardiography, and workup for vitamin B1 deficiency and coronary artery disease as warranted by risk factors. An extensive workup including cardiac magnetic resonance imaging, exercise testing, right-sided catheterization with biopsy, and 24-hour electrocardiography monitoring will uncover only a small number of additional etiologies for DCM.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It was implemented for genetic testing medical review updates starting in 2017 (Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organisation, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. 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

Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is defined as the presence of left ventricular enlargement and dilatation in conjunction with significant systolic dysfunction. Dilated cardiomyopathy has an estimated prevalence of 1 in 2700 in the United States. The age of onset for DCM varies, ranging from infancy to the eighth decade, with most individuals developing symptoms in the fourth through sixth decades.

Idiopathic Dilated Cardiomyopathy

When a patient presents with DCM, a workup is performed to identify underlying causes, especially those treatable. The standard workup consists of a clinical exam, blood pressure monitoring, electrocardiography, echocardiography, and workup for coronary artery disease as warranted by risk factors. An extensive workup including cardiac magnetic resonance imaging (MRI), exercise testing, right-sided catheterization with biopsy, and 24-hour electrocardiography monitoring will uncover only a small number of additional etiologies for DCM.[3,] Approximately 35% to 40% of DCM cases are thus determined to be idiopathic after a negative workup for the secondary causes listed above. This has traditionally been termed idiopathic dilated cardiomyopathy (IDC).

Clustering of IDC within families has been reported, leading to the conclusion that at least some cases of DCM have a genetic basis. Familial DCM is diagnosed when 2 closely related family members have IDC in the absence of underlying causes. Penetrance of familial DCM is variable and age-dependent, often leading to a lack of appreciation of the familial component.

Genetic Dilated Cardiomyopathy

Genetic DCM has been proposed as a newer classification that includes both familial DCM and some cases of sporadic IDC. The percentage of patients with sporadic DCM that has a genetic basis is not well characterized. Most disease-associated variants are inherited in an autosomal dominant fashion, but some autosomal recessive, X-linked, and mitochondrial patterns of inheritance also are present. Expanded numbers of genotyped individuals facilitate genotype-phenotype correlations and studies of natural disease history. Recognition of high-risk variant carriers is important as these individuals would be expected to have the most to gain from pre-emptive interventions.

In general, genotype-phenotype correlations in the inherited cardiomyopathies are either not present or not well characterized. There have been some purported correlations between certain disease-associated variants and the presence of arrhythmias. For example, patients with conduction system disease and/or a family history of sudden cardiac death may be more likely to have disease-associated variants in the lamin A/C (LM), *SCN5A*, and desmin genes. Kayvanpour et al (2017) performed a meta-analysis of genotype-phenotype associations in DCM. The analysis included 48 studies (N=8097 patients) and found a higher prevalence of sudden cardiac death, cardiac transplantation, and ventricular arrhythmias in the LM and phospholamban (PLN) disease-associated variant carriers and increasing penetrance with age of DCM phenotype in subjects with titin (TTN)-truncating variants.

There may be interactions between genetic and environmental factors that lead to the clinical manifestations of DCM. A genetic variant may not in itself be sufficient to cause DCM but may predispose to developing DCM in the presence of environmental factors such as nutritional deficiencies or viral infections. It also has been suggested that DCM genetics may be more complex than single-gene variants, with low-penetrance variants that are common in the population contributing to a cumulative risk of DCM that includes both genetic and environmental factors.

Diagnosis of Dilated Cardiomyopathy

Primary clinical manifestations of DCM are heart failure and arrhythmias. Symptoms of heart failure, such as dyspnea on exertion and peripheral edema, are the most common presentations of DCM. These symptoms are generally gradual in onset and slowly progressive over time. Progressive myocardial dysfunction also may lead to electrical instability and arrhythmias. Symptoms of arrhythmias may include light-headedness, syncope, or sudden cardiac arrest.

Many underlying conditions can cause DCM, including

- Ischemic coronary artery disease
- Toxins
- Metabolic conditions
- Endocrine disorders
- Inflammatory and infectious diseases
- Infiltrative disorders
- Tachycardia-mediated cardiomyopathy.

Treatment of Dilated Cardiomyopathy
Treatment of DCM is similar to that for other causes of heart failure. This includes medications to reduce fluid overload and relieve strain on the heart and lifestyle modifications such as salt restriction. Patients with clinically significant arrhythmias also may be treated with antiarrhythmic medications, pacemaker implantation, and/or an automatic implantable cardiac defibrillator. Automatic implantable cardiac defibrillator placement for primary prevention also may be performed if criteria for low ejection fraction and/or other clinical symptoms are present. End-stage DCM can be treated with cardiac transplantation.

Genetic Testing for Dilated Cardiomyopathy
Approximately 30% to 40% of patients with DCM referred for genetic testing will have a disease-associated variant identified. Disease-associated variants linked to DCM have been identified in more than 40 genes of various types and locations. The most common genes involved are those that code for TTN, myosin heavy chain (*MYH7*), troponin T (*TNNT2*), and alpha-tropomyosin (*TPM1*). These 4 genes account for approximately 30% of disease-associated variants identified in cohorts of patients with DCM. A high proportion of the identified disease-associated variants are rare, or novel, variants, thus creating challenges in assigning the pathogenicity of discovered variants. Some individuals with DCM will have more than 1 DCM-associated variant. The frequency of multiple disease-associated variants is uncertain, as is the clinical significance.

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.

Dilated cardiomyopathy (DCM) is characterized by progressive left ventricular enlargement and systolic dysfunction, leading to clinical manifestations of heart failure. There are a variety of causes of DCM, including genetic and nongenetic conditions. Genetic forms of DCM are heterogeneous in their molecular basis and clinical expression. Genetic testing for DCM has potential utility for confirming a diagnosis of genetic DCM and as a prognostic test in family members when familial DCM is present.

Summary of Evidence

For individuals who have signs and/or symptoms of dilated cardiomyopathy (DCM) who receive comprehensive genetic testing, the evidence includes large case series reporting clinical validity and prospective observational studies reporting clinical utility. Relevant outcomes are overall survival, test validity, symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. The percentage of patients with idiopathic DCM who have a genetic variant (clinical sensitivity) is relatively low, in the range of 10% to 40%. Additional studies assessed clinical outcomes of patients with DCM and at least 1 known variant compared with patients with DCM and no known variants. The studies reported that patients with DCM and known variants experienced lower event-free survival, earlier onset of symptoms, lower transplant-free survival, and more life-threatening arrhythmias compared with patients with DCM and no known variants. A prospective observational study has reported that patients with DCM and known variants experienced high rates of morbidity and mortality during 4 to 8 years of follow-up. While direct evidence of clinical usefulness is lacking, confirming a diagnosis can lead to changes in clinical management, which improve net health outcomes. Changes in management may include earlier implantation of cardiac defibrillators or increased surveillance to detect worsening of symptoms, as well as cascade genetic testing of asymptomatic family members. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic with a first-degree relative who has DCM and a known familial variant who receive targeted genetic testing for a known familial variant, the evidence includes retrospective studies and case series reporting clinical value and a prospective observational study reporting clinical utility. Relevant outcomes are test validity, symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. For an individual at-risk due

to genetic DCM in the family, genetic testing can identify whether a familial variant has been inherited. A prospective observational study with 4 to 8 years of follow-up reported the development of cardiac symptoms among patients initially asymptomatic who had DCM-related variants. While direct evidence of clinical usefulness is lacking, confirming a diagnosis can lead to changes in clinical management, which improve net health outcomes. Changes in management may include periodic clinical and cardiovascular evaluations to detect the earliest signs of disease, as well as genetic counseling. 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.

American Heart Association

In 2016, the American Heart Association (AHA) released a scientific statement regarding diagnostic and treatment strategies for specific dilated cardiomyopathy (DCM), the AHA stated: "A significant proportion of idiopathic DCM cases could have genetic causes and could benefit from genetic screening, especially in familial or suspected cases; however, randomized clinical trials that demonstrate an association of genetic testing for specific disorders with disease-specific gene panels and improvement in clinical outcomes are not available, and this awaits future studies." Table 1 summarizes the AHA recommendations regarding genetic testing for patients with DCM.

Table 1. Genetic Testing Recommendations for Dilated Cardiomyopathy by the American Heart Association

Recommendation	LOE
Mutation-specific genetic testing is recommended for family members and appropriate relatives after the identification of a DCM-causative mutation in the index case.	B

Recommendation	LOE
In patients with familial or idiopathic cardiomyopathy, genetic testing can be useful in conjunction with genetic counseling.	B
Genetic testing can be useful for patients with familial DCM to confirm the diagnosis, to facilitate cascade screening within the family, and to help with family planning.	A
Recommendations for Pediatric DCM	**LOE**
Comprehensive or targeted DCM genetic testing (LMNA and SCN5A) is recommended for patients with DCM and significant cardiac conduction disease (ie, first-, second-, or third-degree heart block) or a family history of premature unexpected sudden death.	A
Mutation-specific genetic testing is recommended for family members and appropriate relatives after the identification of a DCM-causative mutation in the index case.	B
Genetic testing can be useful for patients with familial DCM to confirm the diagnosis, facilitate cascade screening within the family, and help with family planning.	A
In pediatric patients with a DCM phenotype, and musculoskeletal symptoms such as hypotonia, a skeletal muscle biopsy may aid in the diagnosis, and genetic testing may be considered.	C

DCM: dilated cardiomyopathy; LOE: level of evidence.

American College of Medical Genetics and Genomics

In 2018, the American College of Medical Genetics and Genomics (ACMG) published clinical practice recommendations for the genetic evaluation of cardiomyopathy. The following recommendations were made for all types of cardiomyopathy:

- Genetic testing is recommended for the most clearly affected family member.
- Cascade genetic testing of at-risk family members is recommended for pathogenic and likely pathogenic variants.
- In addition to routine newborn screening tests, specialized evaluation of infants with cardiomyopathy is recommended, and genetic testing should be considered.

The ACMG also provided information on specific variants, noting that *TTNtv* represents the most common genetic variant found in DCM (10% to 20% of cases), with *LMNA* being the second most common variant identified (diagnostic yield of 5.5%).

When a cardiovascular phenotype has been identified, the ACMG recommends family-based genetic evaluations and surveillance screening.

Heart Rhythm Society and European Heart Rhythm Association
In 2011, the Heart Rhythm Society and European Heart Rhythm Association issued joint guidelines on genetic testing for cardiac channelopathies and cardiomyopathies.[59,] These guidelines included the following recommendations on genetic testing for DCM and were reaffirmed in 2018 (Table 6).

Table 6. Genetic Testing Recommendations for Dilated Cardiomyopathy by the Heart Rhythm Society and European Heart Rhythm Association

Recommendation	COR
"Comprehensive or targeted (*LM*and *SCN5A*) DCM genetic testing is recommended for patients with DCM and significant cardiac conduction disease (ie, first-, second-, or third-degree heart block) and/or with a family history of premature unexpected sudden death."	I
"Mutation-specific [familial variant] testing is recommended for family members and appropriate relatives following the identification of a DCM-causative mutation in the index case."	I
"Genetic testing can be useful for patients with familial DCM to confirm the diagnosis, to recognize those who are highest risk of arrhythmia and syndromic features, to facilitate cascade screening within the family, and to help with family planning."	IIa

COR: class of recommendation (I: recommended; IIa: can be useful); DCM: dilated cardiomyopathy.

The 2011 Heart Rhythm Society and European Heart Rhythm Association consensus statement also noted that prophylactic implantable cardioverter-defibrillator can be considered in patients with known arrhythmia and/or conduction system disease (LM or Desmin [DES]).

Heart Failure Society of America
In 2018, the Heart Failure Society of America published practice guidelines on the genetic evaluation of cardiomyopathy.[60,] The following recommendations for genetic testing for cardiomyopathy (including DCM) were made:

- "Evaluation, genetic counseling, and genetic testing of cardiomyopathy patients are complex processes. Referral to centers expert in genetic evaluation and family-based management should be considered (Level of Evidence B)."
- "Genetic testing should be considered for the one most clearly affected person in a family to facilitate screening and management."
- "Genetic and family counseling is recommended for all patients and families with cardiomyopathy (Level of Evidence A)."

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
Some currently ongoing and unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03037632	Precision Medicine for Dilated Cardiomyopathy in European and African Ancestry	6500	Apr 2023
NCT04572893	Open-Label Exploratory Study of Oral MYK-491 in Stable Ambulatory Patients With Primary Dilated	24	Jan 2025

	Cardiomyopathy Due to Either MYH7 or TTN Variants		
NCT01736566	The MedSeq Project Pilot Study: Integrating Whole Genome Sequencing Into the Practice of Clinical Medicine	213	Aug 2022
NCT03860454	The Deep Phenotype of Lamin A/C Cardiomyopathy - A Proof-of-Principle Relax-omic Pipeline	150	Feb 2025
NCT03843255	Defining the Genetics, Biomarkers and Outcomes for Dilated Cardiomyopathy: a Prospective Multicentre Observational Study	2000	Jul 2027
Unpublished			
NCT02148926	Clinical and Genetic Examinations of Dilated Cardiomyopathy	4554	Jun 2018 (unknown)
NCT03572569	Risk Stratification in Children and Adolescents with Primary Cardiomyopathy	200	Dec 2020 (unknown)
NCT01857856	PHOspholamban RElated CArdiomyopathy STudy - Intervention (Efficacy Study of Eplerenone in Presymptomatic PLN-R14del Carriers)	84	Oct 2021

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

References

1. Hersheberger RE, Morales A. Dilated Cardiomyopathy Overview. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews. Seattle, WA: University of Washington; 2015.
2. Piran S, Liu P, Morales A, et al. Where genome meets phenome: rationale for integrating genetic and protein biomarkers in the diagnosis and management of dilated cardiomyopathy and heart failure. J Am Coll Cardiol. Jul 24 2012; 60(4): 283-9. PMID 22813604

3. Broch K, Andreassen AK, Hopp E, et al. Results of comprehensive diagnostic work-up in 'idiopathic' dilated cardiomyopathy. Open Heart. 2015; 2(1): e000271. PMID 26468400
4. Hershberger RE, Morales A, Siegfried JD. Clinical and genetic issues in dilated cardiomyopathy: a review for genetics professionals. Genet Med. Nov 2010; 12(11): 655-67. PMID 20864896
5. Lakdawala NK, Winterfield JR, Funke BH. Dilated cardiomyopathy. Circ Arrhythm Electrophysiol. Feb 2013; 6(1): 228-37. PMID 23022708
6. Fatkin D, Huttner IG, Kovacic JC, et al. Precision Medicine in the Management of Dilated Cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol. Dec 10 2019; 74(23): 2921-2938. PMID 31806137
7. Kayvanpour E, Sedaghat-Hamedani F, Amr A, et al. Genotype-phenotype associations in dilated cardiomyopathy: meta-analysis on more than 8000 individuals. Clin Res Cardiol. Feb 2017; 106(2): 127-139. PMID 27576561
8. National Center for Biotechnology Information. Genetic Testing Registry. https://www.ncbi.nlm.nih.gov/gtr/. Accessed December 11, 2022.
9. Kadish A, Dyer A, Daubert JP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med. May 20 2004; 350(21): 2151-8. PMID 15152060
10. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. Jan 20 2005; 352(3): 225-37. PMID 15659722
11. Brodsky GL, Muntoni F, Miocic S, et al. Lamin A/C gene mutation associated with dilated cardiomyopathy with variable skeletal muscle involvement. Circulation. Feb 08 2000; 101(5): 473-6. PMID 10662742
12. MacLeod HM, Culley MR, Huber JM, et al. Lamin A/C truncation in dilated cardiomyopathy with conduction disease. BMC Med Genet. Jul 10 2003; 4: 4. PMID 12854972
13. Olson TM, Michels VV, Thibodeau SN, et al. Actin mutations in dilated cardiomyopathy, a heritable form of heart failure. Science. May 01 1998; 280(5364): 750-2. PMID 9563954
14. Sylvius N, Duboscq-Bidot L, Bouchier C, et al. Mutational analysis of the beta- and delta-sarcoglycan genes in a large number of patients with familial and sporadic dilated cardiomyopathy. Am J Med Genet A. Jul 01 2003; 120A(1): 8-12. PMID 12794684
15. Taylor MR, Slavov D, Ku L, et al. Prevalence of desmin mutations in dilated cardiomyopathy. Circulation. Mar 13 2007; 115(10): 1244-51. PMID 17325244
16. Villard E, Duboscq-Bidot L, Charron P, et al. Mutation screening in dilated cardiomyopathy: prominent role of the beta myosin heavy chain gene. Eur Heart J. Apr 2005; 26(8): 794-803. PMID 15769782

17. Dhandapany PS, Razzaque MA, Muthusami U, et al. RAF1 mutations in childhood-onset dilated cardiomyopathy. Nat Genet. Jun 2014; 46(6): 635-639. PMID 24777450
18. McNair WP, Sinagra G, Taylor MR, et al. SCN5A mutations associate with arrhythmic dilated cardiomyopathy and commonly localize to the voltage-sensing mechanism. J Am Coll Cardiol. May 24 2011; 57(21): 2160-8. PMID 21596231
19. van Rijsingen IA, Nannenberg EA, Arbustini E, et al. Gender-specific differences in major cardiac events and mortality in lamin A/C mutation carriers. Eur J Heart Fail. Apr 2013; 15(4): 376-84. PMID 23183350
20. Herman DS, Lam L, Taylor MR, et al. Truncations of titin causing dilated cardiomyopathy. N Engl J Med. Feb 16 2012; 366(7): 619-28. PMID 22335739
21. Theis JL, Sharpe KM, Matsumoto ME, et al. Homozygosity mapping and exome sequencing reveal GATAD1 mutation in autosomal recessive dilated cardiomyopathy. Circ Cardiovasc Genet. Dec 2011; 4(6): 585-94. PMID 21965549
22. Norton N, Li D, Rieder MJ, et al. Genome-wide studies of copy number variation and exome sequencing identify rare variants in BAG3 as a cause of dilated cardiomyopathy. Am J Hum Genet. Mar 11 2011; 88(3): 273-82. PMID 21353195
23. van der Meulen MH, Herkert JC, den Boer SL, et al. Genetic Evaluation of A Nation-Wide Dutch Pediatric DCM Cohort: The Use of Genetic Testing in Risk Stratification. Circ Genom Precis Med. Oct 2022; 15(5): e002981. PMID 36178741
24. Dalin MG, Engström PG, Ivarsson EG, et al. Massive parallel sequencing questions the pathogenic role of missense variants in dilated cardiomyopathy. Int J Cardiol. Feb 01 2017; 228: 742-748. PMID 27886618
25. Haas J, Frese KS, Peil B, et al. Atlas of the clinical genetics of human dilated cardiomyopathy. Eur Heart J. May 07 2015; 36(18): 1123-35a. PMID 25163546
26. Pugh TJ, Kelly MA, Gowrisankar S, et al. The landscape of genetic variation in dilated cardiomyopathy as surveyed by clinical DNA sequencing. Genet Med. Aug 2014; 16(8): 601-8. PMID 24503780
27. University of Bologna. ws-SNPs&GO. n.d.; http://snps.biofold.org/snps-and-go//index.html. Accessed December 12, 2022.
28. Hirtle-Lewis M, Desbiens K, Ruel I, et al. The genetics of dilated cardiomyopathy: a prioritized candidate gene study of LMNA, TNNT2, TCAP, and PLN. Clin Cardiol. Oct 2013; 36(10): 628-33. PMID 24037902

29. van der Linde IHM, Hiemstra YL, Bökenkamp R, et al. A Dutch MYH7 founder mutation, p.(Asn1918Lys), is associated with early onset cardiomyopathy and congenital heart defects. Neth Heart J. Dec 2017; 25(12): 675-681. PMID 28864942
30. Myers VD, Gerhard GS, McNamara DM, et al. Association of Variants in BAG3 With Cardiomyopathy Outcomes in African American Individuals. JAMA Cardiol. Oct 01 2018; 3(10): 929-938. PMID 30140897
31. Verdonschot JAJ, Hazebroek MR, Derks KWJ, et al. Titin cardiomyopathy leads to altered mitochondrial energetics, increased fibrosis and long-term life-threatening arrhythmias. Eur Heart J. Mar 07 2018; 39(10): 864-873. PMID 29377983
32. Ebert M, Wijnmaalen AP, de Riva M, et al. Prevalence and Prognostic Impact of Pathogenic Variants in Patients With Dilated Cardiomyopathy Referred for Ventricular Tachycardia Ablation. JACC Clin Electrophysiol. Sep 2020; 6(9): 1103-1114. PMID 32972544
33. Millat G, Bouvagnet P, Chevalier P, et al. Clinical and mutational spectrum in a cohort of 105 unrelated patients with dilated cardiomyopathy. Eur J Med Genet. 2011; 54(6): e570-5. PMID 21846512
34. Lakdawala NK, Funke BH, Baxter S, et al. Genetic testing for dilated cardiomyopathy in clinical practice. J Card Fail. Apr 2012; 18(4): 296-303. PMID 22464770
35. Priganc M, Zigová M, Boroňová I, et al. Analysis of SCN5A Gene Variants in East Slovak Patients with Cardiomyopathy. J Clin Lab Anal. Mar 2017; 31(2). PMID 27554632
36. van Rijsingen IA, van der Zwaag PA, Groeneweg JA, et al. Outcome in phospholamban R14del carriers: results of a large multicentre cohort study. Circ Cardiovasc Genet. Aug 2014; 7(4): 455-65. PMID 24909667
37. Hasselberg NE, Edvardsen T, Petri H, et al. Risk prediction of ventricular arrhythmias and myocardial function in Lamin A/C mutation positive subjects. Europace. Apr 2014; 16(4): 563-71. PMID 24058181
38. Hasselberg NE, Haland TF, Saberniak J, et al. Lamin A/C cardiomyopathy: young onset, high penetrance, and frequent need for heart transplantation. Eur Heart J. Mar 07 2018; 39(10): 853-860. PMID 29095976
39. Reddy S, Fung A, Manlhiot C, et al. Adrenergic receptor genotype influences heart failure severity and β-blocker response in children with dilated cardiomyopathy. Pediatr Res. Feb 2015; 77(2): 363-9. PMID 25406899
40. Wasielewski M, van Spaendonck-Zwarts KY, Westerink ND, et al. Potential genetic predisposition for anthracycline-associated cardiomyopathy in families with dilated cardiomyopathy. Open Heart. 2014; 1(1): e000116. PMID 25332820

41. Michels VV, Moll PP, Miller FA, et al. The frequency of familial dilated cardiomyopathy in a series of patients with idiopathic dilated cardiomyopathy. N Engl J Med. Jan 09 1992; 326(2): 77-82. PMID 1727235
42. Grünig E, Tasman JA, Kücherer H, et al. Frequency and phenotypes of familial dilated cardiomyopathy. J Am Coll Cardiol. Jan 1998; 31(1): 186-94. PMID 9426039
43. Baig MK, Goldman JH, Caforio AL, et al. Familial dilated cardiomyopathy: cardiac abnormalities are common in asymptomatic relatives and may represent early disease. J Am Coll Cardiol. Jan 1998; 31(1): 195-201. PMID 9426040
44. Mahon NG, Murphy RT, MacRae CA, et al. Echocardiographic evaluation in asymptomatic relatives of patients with dilated cardiomyopathy reveals preclinical disease. Ann Intern Med. Jul 19 2005; 143(2): 108-15. PMID 16027452
45. Brodt C, Siegfried JD, Hofmeyer M, et al. Temporal relationship of conduction system disease and ventricular dysfunction in LMNA cardiomyopathy. J Card Fail. Apr 2013; 19(4): 233-9. PMID 23582089
46. Huggins GS, Kinnamon DD, Haas GJ, et al. Prevalence and Cumulative Risk of Familial Idiopathic Dilated Cardiomyopathy. JAMA. Feb 01 2022; 327(5): 454-463. PMID 35103767
47. Vissing CR, Espersen K, Mills HL, et al. Family Screening in Dilated Cardiomyopathy: Prevalence, Incidence, and Potential for Limiting Follow-Up. JACC Heart Fail. Nov 2022; 10(11): 792-803. PMID 36328645
48. Stava TT, Leren TP, Bogsrud MP. Molecular genetics in 4408 cardiomyopathy probands and 3008 relatives in Norway: 17 years of genetic testing in a national laboratory. Eur J Prev Cardiol. Oct 18 2022; 29(13): 1789-1799. PMID 35653365
49. Fernlund E, Österberg AW, Kuchinskaya E, et al. Novel Genetic Variants in BAG3 and TNNT2 in a Swedish Family with a History of Dilated Cardiomyopathy and Sudden Cardiac Death. Pediatr Cardiol. Aug 2017; 38(6): 1262-1268. PMID 28669108
50. Asadi M, Foo R, Salehi AR, et al. Mutation in δ-Sg Gene in Familial Dilated Cardiomyopathy. Adv Biomed Res. 2017; 6: 32. PMID 28401079
51. Bodian DL, Vilboux T, Hourigan SK, et al. Genomic analysis of an infant with intractable diarrhea and dilated cardiomyopathy. Cold Spring Harb Mol Case Stud. Nov 2017; 3(6). PMID 28701297
52. Yuan HX, Yan K, Hou DY, et al. Whole exome sequencing identifies a KCNJ12 mutation as a cause of familial dilated cardiomyopathy. Medicine (Baltimore). Aug 2017; 96(33): e7727. PMID 28816949

53. Petropoulou E, Soltani M, Firoozabadi AD, et al. Digenic inheritance of mutations in the cardiac troponin (TNNT2) and cardiac beta myosin heavy chain (MYH7) as the cause of severe dilated cardiomyopathy. Eur J Med Genet. Sep 2017; 60(9): 485-488. PMID 28642161
54. Rafiq MA, Chaudhry A, Care M, et al. Whole exome sequencing identified 1 base pair novel deletion in BCL2-associated athanogene 3 (BAG3) gene associated with severe dilated cardiomyopathy (DCM) requiring heart transplant in multiple family members. Am J Med Genet A. Mar 2017; 173(3): 699-705. PMID 28211974
55. Liu JS, Fan LL, Zhang H, et al. Whole-Exome Sequencing Identifies Two Novel TTN Mutations in Chinese Families with Dilated Cardiomyopathy. Cardiology. 2017; 136(1): 10-14. PMID 27544385
56. Posafalvi A, Herkert JC, Sinke RJ, et al. Clinical utility gene card for: dilated cardiomyopathy (CMD). Eur J Hum Genet. Oct 2013; 21(10). PMID 23249954
57. Bozkurt B, Colvin M, Cook J, et al. Current Diagnostic and Treatment Strategies for Specific Dilated Cardiomyopathies: A Scientific Statement From the American Heart Association. Circulation. Dec 06 2016; 134(23): e579-e646. PMID 27832612
58. Hershberger RE, Givertz MM, Ho CY, et al. Genetic evaluation of cardiomyopathy: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. Sep 2018; 20(9): 899-909. PMID 29904160
59. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm. Aug 2011; 8(8): 1308-39. PMID 21787999
60. Hershberger RE, Givertz MM, Ho CY, et al. Genetic Evaluation of Cardiomyopathy-A Heart Failure Society of America Practice Guideline. J Card Fail. May 2018; 24(5): 281-302. PMID 29567486

Policy History

Original Effective Date: 03/19/2014
Current Effective Date: 07/10/2023

03/06/2014	Medical Policy Committee review
03/19/2014	Medical Policy Implementation Committee approval. New policy.
01/01/2015	Coding Update
03/05/2015	Medical Policy Committee review

03/20/2015	Medical Policy Implementation Committee approval. No change to coverage.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
03/03/2016	Medical Policy Committee review
03/16/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes and CPT coding update
03/02/2017	Medical Policy Committee review
03/15/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/01/2018	Medical Policy Committee review
03/21/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/06/2019	Medical Policy Committee review
06/19/2019	Medical Policy Implementation Committee approval. Title changed from "Genetic Testing for Dilated Cardiomyopathy" to "Genetic Testing for Idiopathic Dilated Cardiomyopathy". Policy statements changed from investigational to medically necessary. Added a *Note* after the second eligible for coverage statement as follows: "*If there is evidence that previous genetic testing for dilated cardiomyopathy was completed, repeated testing is not necessary and is not eligible for coverage.* Added vitamin B1 deficiency to workup for patients with signs and symptoms of dilated cardiomyopathy in the Policy Guidelines.
06/04/2020	Medical Policy Committee review
06/10/2020	Medical Policy Implementation Committee approval. Title changed from "Genetic Testing for Idiopathic Dilated Cardiomyopathy" to "Genetic Testing for Dilated Cardiomyopathy". Coverage eligibility unchanged.
06/03/2021	Medical Policy Committee review
06/09/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/02/2022	Medical Policy Committee review
06/08/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/01/2023	Medical Policy Committee review

Genetic Testing for Dilated Cardiomyopathy

Policy # 00409
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06/14/2023 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date: 06/2024

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2022 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not 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.

CPT is a registered trademark of the American Medical Association.

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

Code Type	Code
CPT	81403, 81405, 81406, 81407, 81439, 81479
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

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*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.

**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.