BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.114 Genetic Testing for Idiopathic Dilated Cardiomyopathy

Annual Effective Policy Date: July 1, 2024

Original Policy Date: March 2014

Related Policies:

2.04.43 - Genetic Testing for Cardiac Ion Channelopathies

Genetic Testing for Idiopathic Dilated Cardiomyopathy

Description

Description

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.

OBJECTIVE

The objective of this evidence review is to examine whether genetic testing improves net health outcomes in individuals with suspected dilated cardiomyopathy and in asymptomatic individuals who have a relative with dilated cardiomyopathy and a known familial variant.

POLICY STATEMENT

Comprehensive genetic testing for individuals with signs or symptoms of dilated cardiomyopathy, which is considered idiopathic after a negative workup for secondary causes, is considered **medically necessary**.

Targeted genetic testing for asymptomatic individuals with a first-degree relative who has dilated cardiomyopathy and a known familial variant is considered **medically necessary**.

Genetic testing for dilated cardiomyopathy is considered **investigational** in all other situations.

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 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 evidence 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<97>"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"<97>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

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

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.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA REGULATORY STATUS

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

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."[59] 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
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.[60] 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.[61,] These guidelines included the following recommendations on genetic testing for DCM and were reaffirmed in 2018 (Table 2).

Table 2. 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]).[61,]

Heart Failure Society of America

In 2018, the Heart Failure Society of America published practice guidelines on the genetic evaluation of cardiomyopathy.[62,] 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.

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 Infomation. GTR: Genetic Testing Registry. n.d.; https://www.ncbi.nlm.nih.gov/gtr/. Accessed December 19, 2023.
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. Hofmeyer M, Haas GJ, Jordan E, et al. Rare Variant Genetics and Dilated Cardiomyopathy Severity: The DCM Precision Medicine Study. Circulation. Sep 12 2023; 148(11): 872-881. PMID 37641966
25. Dalin MG, Engstrm 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
26. 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
27. 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
28. University of Bologna. ws-SNPs&GO. n.d.; http://snps.biofold.org/snps-and-go//index.html. Accessed December 18, 2023.
29. National Center for Biotechnology Information. Genetic Testing Registry. https://www.ncbi.nlm.nih.gov/gtr/. Accessed December 17, 2023.
30. 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
31. van der Linde IHM, Hiemstra YL, Bkenkamp 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

32. 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
33. 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
34. 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
35. 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
36. 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
37. Priganc M, Zigov M, Boroňov I, et al. Analysis of SCN5A Gene Variants in East Slovak Patients with Cardiomyopathy. J Clin Lab Anal. Mar 2017; 31(2). PMID 27554632
38. 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
39. 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
40. 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
41. 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
42. 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
43. 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
44. Grnig E, Tasman JA, Kcherer H, et al. Frequency and phenotypes of familial dilated cardiomyopathy. J Am Coll Cardiol. Jan 1998; 31(1): 186-94. PMID 9426039
45. 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
46. 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
47. 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
48. 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
49. 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
50. 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
51. Fernlund E, sterberg 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
52. 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
53. 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
54. 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
55. 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
56. 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
57. 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
58. 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
59. 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
60. 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
61. 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

62. 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 - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
March 2014	New policy	Genetic testing for dilated cardiomyopathy is considered investigational for all indications
March 2015	Replace policy	Policy updated with literature review; references 5, 18-19, and 21-25 added. Policy statement unchanged
June 2018	Replace policy	Policy updated with literature review through December 11, 2017; references 29, 33-34, and 46-54 added. Policy statement unchanged; summary of evidence updated to reflect FEP benefit application for "existing medical condition€š
June 2019	Replace policy	Policy updated with literature review through December 4, 2018; several references added. Policy statements changed from investigational to medically necessary. Title changed to "Genetic Testing for Idiopathic Dilated Cardiomyopathy"
June 2020	Replace policy	Policy updated with literature review through December 9, 2019; no references added. Policy statement unchanged.
June 2021	Replace policy	Policy updated with literature review through January 2, 2021; references added. Policy statements unchanged.
June 2022	Replace policy	Policy updated with literature review through December 17, 2021; no references added. Policy statement unchanged.
June 2023	Replace policy	Policy updated with literature review through December 9, 2022; references added. Policy statements unchanged.
June 2024	Replace policy	Policy updated with literature review through December 19, 2023; reference added. Policy statements unchanged.