Protocol

Genetic Testing for Idiopathic Dilated Cardiomyopathy

(204114)

Medical Benefit		**Effective Date**: 08/01/19	**Next Review Date**: 05/21
Preauthorization	Yes	**Review Dates**: 05/19, 05/20	

Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With signs and/or symptoms of idiopathic dilated cardiomyopathy	Interventions of interest are: • Comprehensive genetic testing	Comparators of interest are: • Standard workup without genetic testing	Relevant outcomes include: • Overall survival • Test accuracy • Test validity • Symptoms • Change in disease status • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • Who are asymptomatic with a first-degree relative who has dilated cardiomyopathy and a known familial variant	Interventions of interest are: • Targeted genetic testing for a known familial variant	Comparators of interest are: • Standard workup without genetic testing	Relevant outcomes include: • Overall survival • Test accuracy • Test validity • Symptoms • Morbid events • Functional outcomes • Quality of life • Treatment-related morbidity

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.

SUMMARY OF EVIDENCE

For individuals who have signs and/or symptoms of 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 out-

comes, 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 one 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 four to eight 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 a meaningful 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 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 four to eight 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 a meaningful improvement in the net health outcome.

POLICY

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 includes a clinical exam, blood pressure monitoring, electrocardiography, echocardiography, and workup for coronary artery disease as warranted by risk factors. 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 D and serves as an international standard in D diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the HUman Variome Project, the Human Genome Organization, 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 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

Experts recommend formal genetic counseling for patients 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 patients; 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.

BACKGROUND

DIAGNOSIS OF DILATED CARDIOMYOPATHY

Primary clinical manifestations of dilated cardiomyopathy (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 lightheadedness, syncope, or sudden cardiac arrest.

Many underlying conditions can cause DCM, including:[1]

- Ichemic 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.[2] 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 titin (TTN), myosin heavy chain (MYH7), troponin T (TNNT2), and alpha-tropomyosin (TPM1). These four genes account for approximately 30% of disease-associated variants identified in cohorts of patients with DCM.[3] 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 one DCM-associated variant.[2] The frequency of multiple disease-associated variants is uncertain, as is the clinical significance.

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.

RELATED PROTOCOLS

General Approach to Evaluating the Utility of Genetic Panels

Genetic Testing for Cardiac Ion Channelopathies

Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy

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Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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