Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 5/1/22**
(See policy history boxes for previous effective dates)

Title: Genetic Testing for Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D)

Description/Background

The era of molecular genetics has led to the identification of numerous disorders in cardiology that are due to single-gene mutations. These disorders, which are inherited in a Mendelian fashion, can be broadly classified into cardiomyopathies and arrhythmogenic disorders. They are often clinically silent yet associated with serious abnormalities that result in increased cardiac morbidity and mortality. As a result, the potential of genetic testing to identify affected patients early and intervene prior to the onset of cardiovascular events is promising as a means to improve health outcomes.

Arrhythmogenic right ventricular cardiomyopathy (ARVC-also known as arrhythmogenic right ventricular dysplasia-ARVD) is a heritable, progressive cardiomyopathy characterized by ventricular dysfunction and arrhythmias. Up to 20% of sudden cardiac deaths may be attributed to ARVC. The disease may manifest at any age, but typically occurs between the second and fifth decade of life. The exact prevalence is unknown, but is estimated to affect 1 in 5,000 to 1 in 1,250 individuals.

ARVC is associated with a highly variable clinical course and a broad spectrum of symptoms and electrical/structural abnormalities. The symptoms of ARVC are non-specific and include palpitations, syncope, breathlessness and chest pain. Up to 40% of ARVC probands experience sudden cardiac death as their first clinical manifestation. Diagnostic criteria for ARVC have been established and focus on medical history (symptoms and family history), physical exam and diagnostic tests, such as blood tests (genetic testing), electrocardiogram, echocardiogram, exercise stress test, cardiac catheterization, endomyocardial biopsy, CT scan and MRI.

A set of clinical diagnostic criteria for ARVD/C, the International Task Force (ITF) diagnostic criteria, published in 1994 and modified in 2010. For a diagnosis of ARVD/C, a patient must

meet 2 major criteria, 1 major plus 2 minor criteria, or 4 minor criteria from different categories. A summary of the ITF clinical diagnostic criteria is presented in the Inclusionary/Exclusionary Guidelines section of this policy.

The hallmark pathophysiological feature of ARVC is replacement of the right ventricular free wall with fatty and fibrous tissue. However, ARVC may involve both ventricles and occasionally predominantly affects the left ventricle. The earlier stages of the disease can be subclinical with concealed structural abnormalities and can be especially difficult to accurately diagnose.

Since sudden cardiac death is first clinical manifestation for nearly half of ARVC patients, making an early and accurate diagnosis is critical for enabling appropriate treatment, which frequently includes implantation of a cardioverter defibrillator. With an early diagnosis and appropriate treatment, most ARVC patients have an excellent prognosis. The insensitivity of conventional diagnostic tools to diagnose ARVC and differentiate it from other arrhythmic disorders, such as benign idiopathic right ventricular tachycardia, makes genetic testing for ARVC of special importance.

ARVC is typically inherited as an autosomal dominant disease, which means that a single mutation is sufficient to cause the disease and offspring of an individual with ARVC have a 50% risk for inheriting the disease-causing mutation. Genetic testing is intended to provide analysis of the major ARVC genes. The analysis includes sequence determination and variant detection. The genes analyzed by this test include:

- *Desmoplakin (DSP)-encoding desmoplakin,*
- *Plakophillin-2* (*PKP2)-encoding plakophilin-2,*
- *Desmoplakin-2 (DSG2)- encoding desmoglein-2,*
- *JUP (encoding junctional plakoglobin) and*
- *Desmocollin-2* (*DSC2)-(encoding desmocollin-2*.
- *Transmembrane protein 43* (*TMEM43*) is another ARVC causal gene and is associated with a fully penetrant form of ARVC.
- Defects in the *protein kinase* gene (*PKG)*, *ryanodine receptor 2* (*RYR2)* and *transforming growth factor beta-3 precursor* (*TGFB3)* are also associated with ARVC, but are rare causes of ARVC.

Approximately 50% of individuals with ARVD/C who have undergone full sequence analysis of these desmosome genes have a single heterozygous mutation identified, though a few cases of individuals with homozygous or compound heterozygous mutations have also been described. ARVD/C segregates in families with both incomplete penetrance and variable expressivity; clinical screening of family members is recommended, particularly among those recognized to share a genetic predisposition to ARVD/C. Owing to the age-dependent onset of ARVD/C, repeat clinical screening is recommended at 2- to 3-year intervals from the age of 12 years in the absence of a known mutation, to help target family members at highest risk; in families with earlier onset disease or sudden cardiac death in children, earlier clinical screening should be performed.

The testing can be ordered in the following two configurations:

- Comprehensive ARVC analysis: This test provides analysis for variants in five ARVC causal genes and is indicated for cases of suspected ARVC.

- Family specific analysis: This test provides analysis of one or more mutations found in an index case using either one of the above test configurations or confirmed results from another laboratory and is appropriate for testing blood relatives.

Genetic testing for ARVC may be offered in a variety of ways. For example, if a family member has been diagnosed with ARVC based on clinical characteristics, analysis of all five ARVC genes can be performed to identify the specific mutation. If a mutation is identified, additional family members can undergo a focused genetic analysis for the identified mutation.

Genetic testing has revealed multiple different mutations along the length of known ARVC genes. Hundreds of mutations associated with ARVC have been reported. The pathophysiologic significance of each of the discrete mutations is an important part of the interpretation of genetic analysis. The testing laboratory compares the results of this genetic testing to its database of over 400 healthy individuals of diverse ethnic backgrounds who were tested using the same assays to minimize the chance of misinterpreting a harmless background variant as disease-causing. The most informative results occur when a family member undergoes genetic testing after a specific genetic mutation is identified in symptomatic relatives known to have ARVC.

Another factor complicating interpretation of the genetic analysis is the penetrance of a given mutation or the presence of multiple phenotypic expressions. The value of identifying additional patients with ARVC depends largely on the patient's pretest likelihood of disease. For patients with a moderate to high pretest likelihood, the positive predictive value (PPV) of genetic testing will be high and few patients will be misclassified as having ARVC when they do not. The value also depends on whether patients with genetically identified ARVC have similar clinical manifestations of disease as do patients identified by clinical methods.

Medical Policy Statement

The safety and effectiveness of genetic testing for arrhythmogenic right ventricular cardiomyopathy (ARVC) have been established. It may be considered a useful diagnostic option when indicated for patients meeting specified guidelines.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Inclusions:
Genetic testing is appropriate in the following scenarios:

- For individuals who meet the International Task Force (ITF) clinical criteria for having a high likelihood of having ARVC/D, in order to confirm the specific gene mutation. The likelihood of having ARVC/D is determined as follows:
  - Definite likelihood of ARVC: Meets 2 major **OR** 1 major + 2 minor criteria
  - Borderline likelihood of ARVC: Meets 1 major + 1 minor **OR** 3 minor criteria
  - Possible likelihood of ARVC: Meets 1 major **OR** 2 minor

Clinical Diagnostic Criteria for ARVC/D [International Task Force (ITF) guidelines]

Category	Major Criteria	Minor Criteria
Global and/or regional dysfunction and structural alterations	• Severe dilation and reduction of RV EF w/no (or only mild) LV impairment; • Localized RV aneurysms (akinetic or dyskinetic areas w/ diastolic bulging) • Severe segmental dilation of the RV	• Mild global RV dilation and/or EF reduction with normal LV • Mild segmental dilation of the RV • Regional RV hypokinesia
Tissue characterization of walls	• Fibrofatty replacement of myocardium on endometrial biopsy	• N/A
Repolarization abnormalities	• N/A	• Inverted T waves in right precordial leads (V2 and V3 in persons > 12 yrs old in absence of RBBB)
Depolarization/conduction abnormalities	• Epsilon waves or localized prolongation (>110 ms) of the QRS complex in right precordial leads (V1 to V3)	• Late potentials in the signal-averaged ECG
Arrhythmias	• N/A	• LBBB-type ventricular tachycardia (sustained and nonsustained) on ECG, Holter, or exercise testing
Family history	• Familial disease confirmed by necropsy or surgery	• Familial history of premature sudden death (<35 yrs of age) due to suspected ARVD/C • Family history based on clinical diagnosis using present criteria

Key: ECG, electrocardiogram; EF, ejection fraction; LBBB, left bundle branch block; LV, left ventricle; ms, milliseconds; RBBB, right bundle branch block; RV, right ventricle.

- For individuals who do <u>not</u> meet the clinical criteria for ARVC per the ITF guidelines, but who have:
  - A close relative (i.e., a first-, second- or third-degree relative) with a *known* ARVC mutation, **or**
  - A close relative diagnosed with ARVC by clinical means (ITF guidelines) whose genetic status is unavailable, **or**
  - Signs and/or symptoms indicating a moderate-to-high pretest probability of ARVC based on the ITF guidelines.
- For an individual who <u>meets</u> the clinical criteria for ARVC and who has a close relative at risk for ARVC with an indication for genetic testing. In this circumstance, testing of the individual with ARVC is intended to inform genetic testing options for at-risk relatives.

<u>Exclusions</u>:

- Genetic screening for ARVC in the general population is excluded because such screening is considered not medically necessary or of unproven benefit.
- Genetic testing for determining prognosis and/or directing therapy in patients with known ARVC who do not have close relative(s) with indications for genetic testing.
- Next-generation sequencing panels for ARVC.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

81406 81408 81439 81479

Other codes (investigational, not medically necessary, etc.):

N/A

Rationale

The diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC) using routine clinical diagnostic tools is not always possible, as the presentation of the disease is variable and often non-specific. Routine diagnostic tools are not sensitive for detecting the early stages of ARVC and have poor diagnostic accuracy. Molecular diagnosis affords the potential to enhance diagnostic reliability in ARVC syndrome.

A review of sudden cardiac deaths termed "sudden arrhythmic death syndrome" (SADS) was conducted by Behr et al (2008). Of 262 first-degree relatives of 57 people who died of SADS, 184 underwent cardiologic assessment. Thirty (53%) of the 57 families were diagnosed with inherited cardiac disease; 9% of the 57 families were found to have ARVC. The authors concluded that over half of SADS deaths were due to inherited heart disease and that "accurate identification of the diseases is vital for appropriate prophylaxis amongst relatives who should undergo comprehensive cardiologic evaluation, guided and confirmed by mutation analysis."

An article by Awad in 2008 stated that a comprehensive exonic sequence analysis of the known desmosomal ARVD/C-related genes currently identifies a responsible mutation in approximately 50% of ARVD/C probands.[1] Patients and their physicians may seek clinical genetic testing for ARVD/C for several reasons. In our experience, the most common reason cited is identification of individuals related to someone with ARVD/C who may be at increased risk of sudden cardiac death or of developing the disorder. In such cases, the affected proband should be tested first and if a mutation is identified, at-risk family members can also seek testing.

Corrado et al stated, in 2011, that "Advances in the molecular genetics of ARVC/D have provided new insights into the understanding of the pathogenesis and pathophysiology of the disease, showing that in its pure form it is a genetic disorder resulting from defective desmosomal proteins.[8] The availability of molecular testing for screening known gene mutations offers the possibility to identify genetically affected individuals by DNA characterization. The potential clinical impact of genotype determination includes early diagnosis with prediction of clinical phenotype, arrhythmic risk stratification and therapeutic interventions aimed at preventing sudden death.

Results of genetic testing for ARVC can be useful in directing the testing of first-degree relatives and develop preventive measures to avoid serious cardiovascular events. In 1994 an International Task Force proposed criteria to facilitate and standardize the clinical diagnosis of ARVC/D. The proposed strategy consists of reaching a clinical diagnosis by combining multiple sources of diagnostic information such as genetic, ECG, arrhythmic, morphofunctional and histopathological findings. In 2006, evidence-based practice guidelines were published by the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (ACC/AHA/ESC) regarding management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

The guidelines note that, "Genetic analysis is useful in families with RV cardiomyopathy, because whenever a pathogenetic mutation is identified, it becomes possible to establish a presymptomatic diagnosis of the disease among family members and to provide them with genetic counseling to monitor the development of the disease and to assess the risk of transmitting the disease to offspring." Gene mutation analysis and cascade screening of relatives offers an alternative strategy to serial non-invasive cardiac evaluation of families at risk for ARVC/D. While molecular genetic testing supports a clinical overt or suspicious diagnosis for ARVC/D, the results alone cannot confirm the diagnosis. A positive genetic result can only be part of a more comprehensive clinical approach combining multiple sources of diagnostic information such as ECG changes, ventricular arrhythmias and RV morphofunctional/histopathological changes as well as clinical and molecular genetic findings.

Early detection of ARVC/D and preventive therapy of young individuals at highest risk of experiencing sudden cardiac death may be improved by molecular genetic screening within affected families and may alter the clinical management of patients. The diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC) has evolved from pathological assessment at postmortem to a recognizable clinical condition during life for which management of preventative complication (e.g., sudden cardiac death) can be implemented.

Phillips and Cheng reviewed recent advances in the diagnosis and management of ARVC/D. The authors concluded that ARVC is predominantly associated with mutations in desmosomal genes with incomplete penetrance and variable expressivity. Ventricular electrical instability is the hallmark of ARVC, often occurring before structural abnormalities. Goals in the evaluation and management of ARVC are early diagnosis, risk stratification for sudden cardiac death, minimizing ventricular arrhythmias, and delaying the progression of disease.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

Heart Failure Society of America

The Heart Failure Society of America has issued guidelines for the genetic evaluation of cardiomyopathy that includes ARVD/C. The guidelines make the following recommendations.[17]

- A family history for 3 or more generations should be recorded for all patients suspected of having ARVD/C.
- Clinical screening for cardiomyopathy in asymptomatic at-risk relatives of those with ARVD/C should be performed.

- For asymptomatic individuals known to carry a pathogenic sequence variant that causes ARVD/C, clinical screening is recommended yearly between 10 and 50 years of age.
- For asymptomatic at-risk relatives of a patient with ARVD/C for which genetic testing is negative or has not been performed, clinical screening should begin at 10 years of age and be repeated every 3 to 5 years.
- At-risk relatives of an individual with ARVD/C who have any clinical screening test abnormality should be considered for repeat clinical screening after 1 year.
- Genetic testing of the individual in a family who is most clearly affected with ARVD/C should be considered. Genes tested for ARVD/C should be DSC2, DSG2, DSP, and PKP2.

Government Regulations
National/Local:

Medicare does not routinely cover preventive services (unless authorized specifically by Congress). Therefore, coverage for many genetic tests and services, which may be considered preventive, may not be granted under Medicare.

Medicare does not have a policy specifically addressing genetic testing for ARVC. However, the current codes being used to bill for this testing are payable if the ordering physician determines that they are medically necessary.

PGxHealth is also an approved Medicare provider and the *FAMILION* ARVC test is reimbursed by Medicare

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Genetic Testing and Counseling
- Genetic Testing for Hypertrophic Cardiomyopathy
- Genetic Testing for Cardiac Channelopathies

References

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through January 2022, the date the research was completed.

BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/1/10	1/4/10	12/8/09	Joint policy established
3/1/12	12/13/11	12/21/11	Routine maintenance, references added. Rearranged inclusionary section to make more user-friendly.
1/1/14	10/17/13	10/25/13	New molecular pathology codes added to policy; no change in policy status.
1/1/15	10/24/14	11/3/14	No change in policy status. Updated references.
1/1/16	10/13/15	10/27/15	Routine maintenance—CPT code nomenclature updated. No change in policy status.
1/1/17	10/11/16	10/11/16	Routine maintenance, updated rationale and references. No change in policy status.
5/1/17	2/21/17	2/21/17	Added code 81439 as established effective 1/1/17.
5/1/18	2/20/18	2/20/18	Routine policy maintenance. No change in policy status.
5/1/19	2/19/19		Routine policy maintenance. No change in policy status.
5/1/20	2/18/20		Routine policy maintenance. No change in policy status.
5/1/21	2/16/21		Routine policy maintenance – Nomenclature updated for CPT code 81439. No change in policy status.
5/1/22	2/15/22		Routine policy maintenance, no change in policy status.

Next Review Date: 1st Qtr. 2023

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY/DYSPLASIA (ARVC/D)

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply.
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.
- Duplicate (back-up) equipment is not a covered benefit.