

Arrhythmogenic Right Ventricular Cardiomyopathy

Disease State Overview

According to the Centers for Disease Control and Prevention, each year in the United States, more than 600,000 people die from heart disease. Approximately 22,000 of those deaths occur in young, seemingly healthy people ≤ 44 years of age. Arrhythmogenic right ventricular cardiomyopathy (ARVC) accounts for up to 20% of people who experience sudden cardiac death.¹ Approximately 40% of people with ARVC suffer sudden cardiac death as their first clinical manifestation of the disease.^{1,2,3} This startling statistic makes successfully diagnosing ARVC early in its disease process essential to saving lives. ARVC is estimated to affect between 1 in 5,000 to 1 in 1,250 people.^{4,5}

ARVC presents clinically as dilation of the right ventricle and/or fatty infiltration of either ventricle (Figure 1). The pathogenesis of ARVC is characterized by myocyte separation and replacement of the

Figure 1: ARVC Heart Tissue From Triangle of Dysplasia

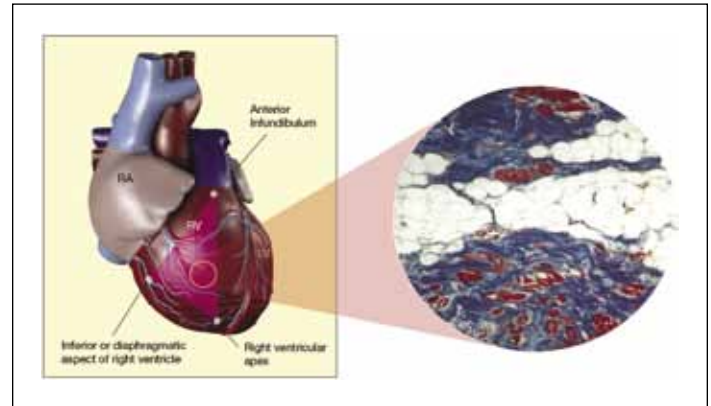
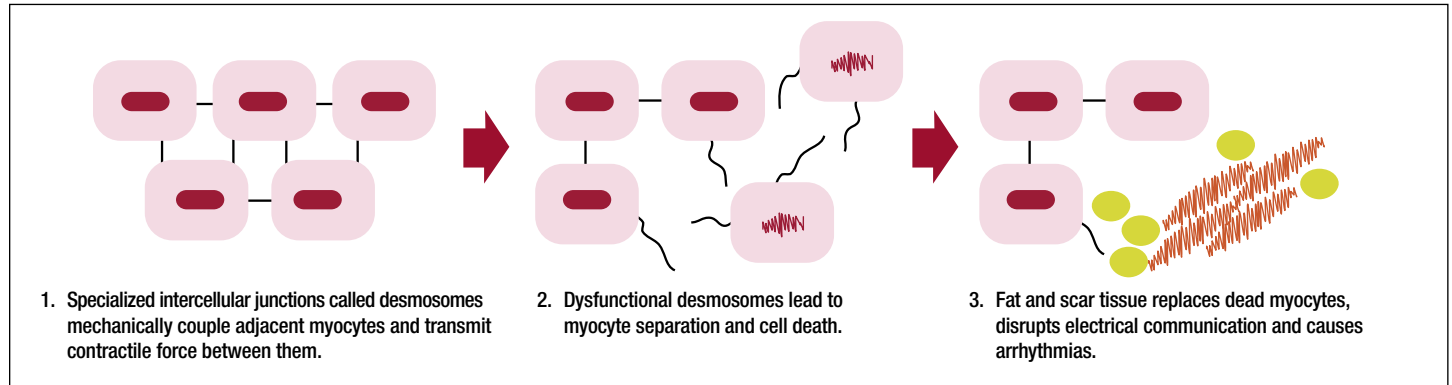


Figure 2: ARVC Pathophysiology



myocardium with fat and fibrosis. This process impairs cell-to-cell electrical signaling and may cause fatal arrhythmias (Figure 2).⁶ The symptoms associated with ARVC include heart palpitations, syncope, chest pain, breathlessness, intolerance to exercise and sudden cardiac death.⁶

The Genetic Cause of ARVC

ARVC is a genetically heterogeneous monogenic disease that is usually inherited as an autosomal dominant trait.⁶ Currently, more than 6 ARVC-susceptibility genes have been identified, most of which code for proteins of the structural unit (desmosome) responsible for keeping myocytes connected and aligned. Approximately 40-50% of patients suspected of having ARVC will have a mutation in 1 of 5 genes.¹ These genes cumulatively account for nearly 100% of the known genetic causes of ARVC (Figure 3).¹

Figure 3: ARVC Genes

Gene	Protein
<i>DSP</i>	Desmoplakin
<i>PKP2</i>	Plakophilin 2
<i>DSG2</i>	Desmoglein 2
<i>DSC2</i>	Desmocollin 2
<i>TMEM43</i>	Transmembrane Protein 43

Challenges Diagnosing ARVC

Making an accurate diagnosis of ARVC based solely on clinical criteria can be difficult. In 1994 the Task Force of the Working Group of Myocardial and Pericardial Disease of the European Society of Cardiology and the Scientific Council of Cardiomyopathies published the first set of guidelines to help direct the accurate diagnosis of ARVC. These criteria were never prospectively validated and lacked sensitivity for diagnosing early-stage and pre-symptomatic/asymptomatic ARVC.^{6,7} In 2010 Marcus et al. published modifications to the 1994 guidelines.⁸ This was done to incorporate new knowledge and technology that would improve diagnostic sensitivity, while maintaining a high degree of specificity.⁸ The 1994 and 2010 guidelines use the same methodology for classifying structural, histological, electrocardiographic, arrhythmic, and genetic features as either Major or Minor criteria. The addition of a pathogenic ARVC-mutation as a Major criterion was one of the most significant additions to the 2010 guidelines. Some challenges include:

1. There Is NO SINGLE Criterion for Diagnosing ARVC

- Diagnosing ARVC may require multiple non-invasive and invasive tests, all of which may be inconclusive.^{1,6}
- Figure 4 shows percentages of ARVC patients fulfilling selected ARVC diagnostic criteria. Major criteria (blue) lack sensitivity and/or specificity while minor criteria (red) lack specificity.¹

2. The Clinical Presentation of ARVC Is Diverse and Non-specific

- ARVC is associated with a highly variable clinical course and a broad spectrum of symptoms and ECG abnormalities.^{1,6,9}

3. The Differential Diagnosis of ARVC Can Be Difficult

- Idiopathic Ventricular Tachycardia (IVT) presents similarly to early-stage ARVC.⁴ Differentiating IVT from ARVC is important because ARVC is often treated with an implantable cardioverter defibrillator, while IVT is not familial and is generally benign.
- ARVC may present with right-dominant, left-dominant or biventricular signs and symptoms. This complicates the differential diagnosis between ARVC and dilated cardiomyopathy (DCM).^{1,6}

4. Over Reliance on Cardiac MRI May Cause Misdiagnosis

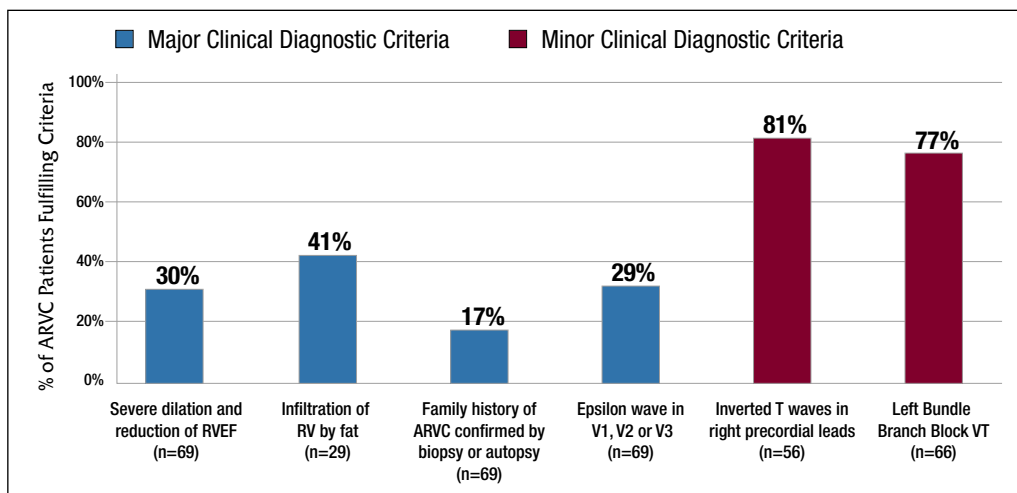
- A study published by researchers at Johns Hopkins University revealed that up to 73% of ARVC diagnoses are made in error.⁹
- The high rate of misdiagnosis is attributed to incomplete testing, over-reliance on the presence of intramyocardial fat and wall thinning on MRI and lack of awareness of diagnostic criteria.⁹

Genetic Analysis May Be Needed for Accurate Diagnosis of Early-stage ARVC

With early diagnosis and appropriate treatment most ARVC patients have an excellent prognosis.¹ However, during early-stage ARVC, patients may not consistently exhibit signs or symptoms of the disease but remain at risk for sudden cardiac arrest during unpredictable periods of disease progression called 'hot phases'.⁶

Genetic analysis is a significant tool for identifying patients with early-stage disease, this is particularly important when clinical criteria are ambiguous or for identification of at-risk family members.

Figure 4: Diagnostic Uncertainty in ARVC



Adapted from: Dalal D, et al. Arrhythmogenic right ventricular dysplasia: a United States experience. *Circulation*. 2005;112:3823-3832.

The **FAMILION ARVC Test**

The **FAMILION ARVC Test** sequences 5 ARVC genes (Figure 5). The test is indicated for:

- Patients with clinical features consistent with the diagnosis of ARVC.
- Relatives of a patient with a known ARVC gene mutation.

A mutation will be found in approximately 40-50% of patients with a high index of suspicion for ARVC.¹

The Role of the **FAMILION ARVC Test**

The **FAMILION ARVC Test** helps eliminate diagnostic uncertainty independent of disease stage or clinical presentation. Genetic analysis may provide the following benefits:

- Disease diagnosis or confirmation of diagnosis
- Interpretation of borderline clinical findings
- Identify at-risk family members
- Establish the need and schedule for clinical surveillance of family members
- Better enable genetic counseling

2010 Diagnostic Guidelines - Identification of a Pathogenic Gene Mutation is a MAJOR Diagnostic Criterion for ARVC

A pathogenic gene mutation combined with any other MAJOR diagnostic criterion from another category is sufficient for making a diagnosis of ARVC.⁸

Genetic Evaluation of Cardiomyopathy - A Heart Failure Society of America (HFSA) Practice Guideline (2009)

The HFSA published a comprehensive assessment of the value of genetic testing for cardiomyopathies including ARVC. Letter grades were based on clinical validity and utility. A letter grade of 'A' corresponds to the highest score while 'C' is the lowest. The HFSA guideline supported genetic testing of an ARVC proband with its highest grade (Figure 6).¹⁰

Figure 6: HFSA Grade for Genetic Testing of Proband

Genetic testing should be considered for the one most clearly affected person in a family to facilitate family screening and management.	
Cardiomyopathy Phenotype	Level of Evidence
Arrhythmogenic right ventricular dysplasia (ARVD)	A

HFSA Supports Genetic Screening of ARVC Families

If a family member is mutation-negative, then their risk of developing ARVC is significantly reduced. For those that are mutation-negative, HFSA recommends that there is NO need for ongoing clinical screening.¹⁰

ACC/AHA/ESC Guidelines (2006) Support Genetic Testing for Identification of ALL Mutation Carriers in an ARVC Family

“Genetic analysis is useful in families with RV cardiomyopathy, because whenever a pathogenic genetic 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.”¹¹

Figure 5: The **FAMILION ARVC Test**

Gene	Protein
<i>DSP</i>	Desmoplakin
<i>PKP2</i>	Plakophilin 2
<i>DSG2</i>	Desmoglein 2
<i>DSC2</i>	Desmocollin 2
<i>TMEM43</i>	Transmembrane Protein 43



PGxHealth Laboratory Process Highlights

PGxHealth sequences 5 genes associated with ARVC.

The following laboratory processes are among the reasons PGxHealth is a leader in genetic testing:

- Two technologists independently score all sequence variants, and a supervisor reconciles any discrepancy.
- All traces with variants are reviewed and approved by an American Board of Medical Genetics board-certified molecular geneticist.
- For each class I or II mutation found, a second round of PCR amplification and sequencing are completed to confirm the initial finding.
- Identified variants are interpreted with respect to an ethnically diverse reference population of several hundred unrelated individuals (presumed non-cardiomyopathy), a database of known mutations and published medical literature (Figure 7).

Figure 7: The *FAMILION* Test Variant Classification

Class I Mutation: Deleterious and Probable Deleterious Mutations
Class II Mutation: Variant of Uncertain Significance
Class III Variant: Variant Not Generally Expected to Cause Disease
Class IV Variant: Non-protein-altering Variant

PGxHealth Reimbursement Highlights

- PGxHealth is an approved Medicare provider.
- PGxHealth is an approved Medicaid provider in most states. PGxHealth reserves the right not to participate in any state's Medicaid program even if approved as a provider.
- A brief list of select insurance companies that have developed positive medical policies for all or select *FAMILION* tests include: CBBSA, United, Aetna, Cigna and Humana.

Every Test Report is Accompanied by an Interpretation Guide

- All test reports include a test-specific interpretation guide. These were developed to better explain the system employed by PGxHealth for rating variants (Figure 8).

Figure 8: The *FAMILION* Tests Interpretation Guide

	← Related to Disease	Not Related to Disease →	
	Class I Mutation (Deleterious or Probable Deleterious)	Class II Mutation (Variant of Uncertain Significance)	Class III Variants (Not Expected to Cause Disease)
Clinical Interpretation	<ul style="list-style-type: none"> • Result strongly suggests an inherited cardiac disease. 	<ul style="list-style-type: none"> • Mutation may be disease-causing or benign. 	<ul style="list-style-type: none"> • Class III variants are not expected to be disease-causing. A report with only Class III variants is considered negative.
Reasons for Classification	<ul style="list-style-type: none"> • Strong evidence of deleteriousness. • “Probable,” if included, indicates that variant is predicted, but has not been demonstrated, to cause disease. • Typically absent from a healthy control population. 	<ul style="list-style-type: none"> • Evidence is insufficient to determine whether the mutation is deleterious. • Typically absent from a healthy control population. 	<ul style="list-style-type: none"> • Evidence indicates variant is not disease-causing. • Typically common in a healthy control population.
Recommendations	<ul style="list-style-type: none"> • Genetic testing of all first-degree relatives is recommended to identify those at risk for disease. Genetic counseling should be considered. 	<ul style="list-style-type: none"> • Genetic testing and clinical screening in family members may elucidate the significance of the mutation. Genetic counseling should be considered. 	<ul style="list-style-type: none"> • Genetic testing of family members for Class III variants is not advised.

The **FAMILION** Family of Genetic Tests

Cardiac Channelopathies	Genes*				Clinical Sensitivity†
LQTS Test	<i>KCNQ1</i> (LQT1) <i>KCNE2</i> (LQT6) <i>SCN4B</i> (LQT10)	<i>KCNH2</i> (LQT2) <i>KCNJ2</i> (LQT7) <i>AKAP9</i> (LQT11)	<i>SCN5A</i> (LQT3) <i>CACNA1C</i> (LQT8) <i>SNTA1</i> (LQT12)	<i>KCNE1</i> (LQT5) <i>CAV3</i> (LQT9)	75-80% ^{1,2}
BrS Test	<i>SCN5A</i> <i>SCN1B</i>	<i>GPD1L</i> <i>KCNE3</i>	<i>CACNA1C</i> <i>SCN3B</i>	<i>CACNB2</i>	25-40% ^{3,4,5,6,7,8,9}
CPVT Test	<i>RYR2</i>	<i>KCNJ2</i>			65-75% ^{10,11,12,13}
SQTS Test	<i>KCNH2</i>	<i>KCNQ1</i>	<i>KCNJ2</i>		Unknown
Cardiomyopathies	Genes*				Clinical Sensitivity†
ARVC Test	<i>DSP</i> <i>PKP2</i>	<i>DSG2</i> <i>DSC2</i>	<i>TMEM43</i>		40-50% ¹⁴
DCM Test	<i>LMNA</i> <i>ANKRD1</i> <i>TNNC1</i>	<i>SCN5A</i> <i>TPM1</i> <i>MYBPC3</i>	<i>ACTC</i> <i>LDB3</i> <i>PLN</i>	<i>MYH7</i> <i>TNNT2</i> <i>TNNI3</i>	~25% ^{2,15}
CD-DCM Test	<i>LMNA</i>	<i>SCN5A</i>			40-50% ^{16,17}
HCM Test	<i>MYH7</i> <i>TPM1</i> <i>MYBPC3</i>	<i>TNNC1</i> <i>TNNT2</i> <i>TNNI3</i>	<i>ACTC</i> <i>MYL2</i> <i>MYL3</i>	<i>GLA</i> <i>LAMP2</i> <i>PRKAG2</i>	50-60% ¹⁸

* See the **FAMILION** test specification sheet for coverage areas. † Percent of patients with a high index of suspicion for the cardiac syndrome that will have a mutation identified.

FAMILION Tests Table References:

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