



## Test Information Sheet

### Cardiology Genetics: Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) Panel

**Also known as:** Arrhythmogenic Right Ventricular Dysplasia (ARVD); Uhl Anomaly; Right Ventricular Dysplasia

**Mendelian Inheritance in Man Number:** ARVC2=600996; ARVC5=604400; ARVC8=607450; ARVC9=609040; ARVC10=610193; ARVC11=610476; ARVC12=611528<sup>1</sup>

#### Clinical Features:

Arrhythmogenic right ventricular cardiomyopathy (ARVC), also known as arrhythmogenic right ventricular dysplasia (ARVD), is a potentially life-threatening heart muscle disease that can cause sudden cardiac death in young persons and athletes. ARVC is a disorder of the cardiac desmosome – protein complexes that maintain cell-to-cell connections and provide mechanical attachments among adjacent cells. Myocyte death and replacement by fat and fibrous tissue in the right ventricle are the pathologic hallmarks of the disease, which may predispose to ventricular tacharrhythmia and sudden cardiac death. The disease prevalence is estimated at 1:1000 to 1:2500, but may be higher in certain populations and because of non-diagnosed or misdiagnosed cases. Patients with ARVC typically develop symptoms between the second and fifth decade of life (mean age at diagnosis 31 years), however onset and severity are widely variable<sup>2,3</sup>.

The most common presenting symptoms of ARVC are heart palpitations, syncope, and sudden cardiac death. Many patients may be asymptomatic and be diagnosed by routine electrocardiogram (ECG). Diagnosis is based on clinical findings, a combination of noninvasive and invasive testing, and family history. Diagnostic criteria were established by McKenna et al in 1994. The diagnostic approach includes the collection of various types of diagnostic information, including genetic, electrocardiographic, and functional findings<sup>4</sup>.

#### Inheritance Pattern:

ARVC is inherited in an autosomal dominant manner, where by definition an affected individual with a disease-causing mutation has a 50% chance of transmitting the mutation to their child. ARVC has been seen to exhibit incomplete penetrance and variable expressivity among families.

#### Genetics:

ARVC is genetically heterogeneous with mutations in at least seven genes being identified to date. These genes include RYR2, TMEM43, DSP, PKP2, DSG2, DSC2 and JUP. Five of these genes (DSP, PKP2, DSG2, DSC2, and JUP) encode desmosomal proteins, while the other two (RYR2 and TMEM43) encode proteins that maintain calcium homeostasis.<sup>2</sup> The majority of individuals with ARVC have a mutation in the genes PKP2 and DSG2 coding for the desmosomal proteins plakophilin-2 and desmoglein-2. Some disease-causing mutations in ARVC may have a reduced penetrance and variable clinical expressivity, even within families. Molecular genetic testing makes it possible to confirm a clinical diagnosis in a symptomatic individual as well as to identify asymptomatic family members at risk for ARVC.

Genotype	Gene	Protein Name
ARVC2	RYR2	Ryanodine receptor 2
ARVC5	TMEM43	Transmembrane protein 43
ARVC8	DSP	Desmoplakin
ARVC9	PKP2	Plakophilin-2
ARVC10	DSG2	Desmoglein-2
ARVC11	DSC2	Desmocollin-2
ARVC12	JUP	Junction plakoglobin

#### Reasons for Referral:

1. Confirmation of a clinical diagnosis in symptomatic patients
2. Risk assessment of asymptomatic family members of a proband with ARVC
3. Genetic counseling and recurrence risk calculation
4. Differentiation of hereditary ARVC from other acquired or genetic heart conditions
5. Prenatal diagnosis in families with a known mutation

**Test Method:**

Using genomic DNA obtained from a blood specimen (2-5 mL in EDTA), the entire coding region of seven genes (RYR2, TMEM43, DSP, PKP2, DSG2, DSC2, and JUP) and their splice junctions are sequenced using a novel solid-state sequencing-by-synthesis process that allows sequencing a large number of amplicons in parallel.<sup>5</sup> For analysis, DNA sequence is assembled and compared to the published genomic reference sequences. The presence of any potentially disease-associated sequence variant(s) is confirmed by conventional dideoxy DNA sequence analysis. A reference library of at least 800 alleles is used to evaluate the frequency of novel sequence variants if indicated. If appropriate, testing of one affected relative or, if not available, of both biological parents, is performed to clarify variants of unknown significance at no additional charge.

**Test Sensitivity:**

The exact percentage of individuals with ARVC who will have a disease-causing mutation that can be identified by sequencing of the seven genes tested for in this panel is currently unknown. It is estimated that this panel would detect a disease-causing mutation in at least 42% of patients with ARVC<sup>2</sup>. The technical sensitivity of this testing approach is estimated to be 98% for mutations identifiable by sequence analysis. Gross deletions and duplications would not be identified using this method.

**Specimen Requirements and Shipping/Handling:**

- Blood: A single tube with 2-5 mL whole blood in EDTA. Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated for 7 days prior to shipping.
- Buccal Brushes: CANNOT be accepted.
- Other Specimens: Contact us for specific inquiries and specimen requests.
- Prenatal Diagnosis: Available only if a familial mutation has been identified. Contact us for more information.

**Required Forms:**

- Cardiology Sample Submission (Requisition) Form – complete all pages
- Payment Options Form or Institutional Billing Instructions
- We highly recommend submitting relevant clinical information (ECG Reports, clinic notes, etc) with each sample.

**CPT Codes and Turn-Around-Times:**

Test #	Description	CPT codes	Turnaround time
385	ARVC panel in a new patient	83891x1, 83900x1, 83901x51, 83904x51, 83909x3, 83912x1	Approx. 8 weeks
901	DNA testing of a relative for a single known mutation	83891x2, 83898x2, 83894x2, 83904x4, 83892x2, 83912x2	Approx. 3 weeks
902	Prenatal diagnosis for a known mutation	83891x5, 83898x10, 83894x5, 83904x10, 83892x2, 83912x5	Approx. 2 weeks

**Possible ICD9 Codes:** Conduction disorder unspecified = 426.9  
Cardiac Dysrhythmia unspecified = 427.9 Cardiac Dysrhythmias = 427

**References Cited:**

1. Online Mendelian Inheritance in Man. [www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM](http://www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM)
2. GeneReviews: Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy. McNally E, MacLeod H, and Dellefave L. <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=arvd> Accessed September 18, 2009.
3. Nava A, Bauce B, Basso C, Muriago M, Rampazzo A, Villanova C, Daliento L, Buja G, Corrado D, Danielli GA, Thiene G. Clinical profile and long-term follow-up of 37 families with arrhythmogenic right ventricular cardiomyopathy. *J Am Coll Cardiol.* 2000; 36: 2226-33. (PubMed: 11127465)
4. McKenna WJ, Thiene G, Nava A, Fontaliran F, Blomstrom-Lundqvist C, Fontaine G, Camerini F. Diagnosis of arrhythmogenic right ventricular dysplasia / cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. *Br Heart J.* 1994; 71: 215-8 (PubMed: 8142187)
5. Bennett S. Pharmacogenomics. 5(4):433-8, 2004 (PubMed: 15165179)

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