Test Specific Guidelines

Arrhythmogenic Right Ventricular Cardiomyopathy Genetic Testing

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Introduction

Genetic testing for arrhythmogenic right ventricular cardiomyopathy is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
ARVC Gene Analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
ARVC Known Familial Mutation Analysis	81403
ARVC Multigene Panel (5 or more genes)	81439

What Is Arrhythmogenic Right Ventricular Cardiomyopathy?

Definition

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC, formerly called Arrhythmogenic Right Ventricular Dysplasia, or ARVD) is a form of heart disease characterized by fibrofatty tissue replacement of the myocardium over time. This typically leads to right sided heart dysfunction.

Incidence

ARVC occurs in 1/1000 to 1/5000 people.[1] This condition is more common in the Italian population (1/200). It may be underdiagnosed, as symptoms can be mild and some individuals are asymptomatic.[2]

Symptoms

ARVC most commonly presents as a cardiac arrhythmia manifested by syncope or palpitations. Sudden death can be a presenting symptom, especially in young athletes.[1,3] Both ECG and cardiac imaging are typically abnormal. Although the right ventricle is most commonly involved, left ventricular abnormalities have been reported. Individuals may progress to cardiomyopathy and heart failure, with approximately 5% requiring heart transplant.[2] The average age at diagnosis is 31 years; however, symptoms can begin in the second decade of life.[2]

Variable expressivity and reduced penetrance have been reported.

Cause

ARVC is caused by replacement of myocardium by fibrofatty tissue. Approximately 40% of ARVC has a genetic cause.[4] Non-genetic causes include sarcoidosis and myocarditis.[1] Mutations in the six common genes (DSC2, DSG2, DSP, JUP, PKP2, and TMEM43) account for a vast majority of cases.[2,5] Sequence variants are most common though deletions/duplication are common in DSP (up to 8%) and PKP2 (11%).[2]

Inheritance

Most cases of ARVC are inherited in an autosomal dominant pattern. Digenic inheritance (pathogenic mutations in two separate genes) has been reported in 4-47% of individuals.[2] These individuals are reported to have more severe arrhythmia. Several autosomal recessive syndromes caused by ARVC genes have also been described. These individuals typically have ARVC with skin and hair findings. Few genotype-phenotype correlation exists, with DSP mutations more commonly causing left ventricular involvement and PKP2 mutations more frequently associated with ventricular tachycardia.[4] Data relating genotype to arrhythmia risk is limited and not currently sufficient for clinical correlation.[5]

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Autosomal recessive inheritance

In autosomal recessive inheritance, individuals have 2 copies of the gene and an individual typically inherits a gene mutation from both parents. Usually only siblings are at risk for also being affected. Males and females are equally affected. Individuals who inherit only one mutation are called carriers. Carriers do not typically show symptoms of the disease, but have a 50% chance, with each pregnancy, of passing on the mutation to their children. If both parents are carriers of a mutation, the risk for each pregnancy to be affected is 1 in 4, or 25%.

Diagnosis

Diagnostic criteria for ARVC have been established and are based on major and minor criteria broken down by image modality.[3]

Major criteria include:[3]

2D echo

- **Right ventricular akinesia, dyskinesia, or aneurysm AND**
- **Parasternal long axis right ventricular outflow tract (RVOT) greater than 31mm; corrected for body surface area OR**
- **Parasternal short axis RVOT greater than 35mm corrected for body surface area OR**
- **Fractional area change less than 34%**

MRI

- **Regional RV akinesia or dyskinesia or dyssynchronous RV contraction; AND**
- **Ratio of RV end-diastolic volume to BSA greater than or equal to 110mL/m^2 (male) or greater than or equal to 100 mL/m^2 (female) OR**
- **RV ejection fraction less than or equal to 40%**

Right ventricular angiography

- **Regional RV akinesia, dyskinesia, or aneurysm**

Minor criteria include:[3]

2D echo

- Regional right ventricular akinesia or dyskinesia; AND
- PLAX RVOT greater than or equal to 29 to less than 32 mm; corrected for BSA OR
- PSAX RVOT greater than or equal to 32 to less than 36 mm; corrected for BSA OR
- Fractional area change greater than 33% to less than or equal to 40%

MRI

- Regional RV akinesia or dyskinesia or dyssynchronous RV contraction; AND
- Ratio of RV end-diastolic volume to BSA greater than or equal to 100 to less than 110 mL/m^2 (male) or greater than or equal to 90 to less than 100 mL/m^2 (female) OR
- RV ejection fraction greater than 40% to less than or equal to 45%

Other diagnostic criteria, which may include both major and minor criteria:[2]

- Electrocardiogram abnormalities
- Endomyocardial biopsy (or autopsy) finding of residual myocytes below 60% and fibrous replacement of the right ventricle in at least one sample
- Family history
- Presence of a pathogenic gene mutation (considered a major criterion)[2]
- Non genetic causes need to be excluded

Clinical Diagnosis

The following table lists criteria needed to determine a clinical diagnosis and the strength of each diagnosis.[3]

Strength of the Diagnosis	Made by the presence of:
Definitive Diagnosis	2 major criteria, or 1 major and 2 minor criteria (from different categories), or 4 minor criteria (from different categories)
Borderline diagnosis	1 major and 1 minor criteria, or 3 minor criteria (from different categories)

Strength of the Diagnosis	Made by the presence of:
Possible diagnosis	1 major criterion, or 2 minor criteria (from different categories)

Management

ARVC management is based on presentation and focuses on avoidance of syncope, cardiac arrest, and sudden death through medication or cardioverter-defibrillator implantation. Heart transplant is occasionally required. Affected individuals are counseled to avoid rigorous physical activity, including competitive sports.[2] Additionally, evidence exists to suggest testing symptomatic minors or testing minors for a known familial disease-causing mutation can change their management and prevent sudden cardiac death.[1,4]

Survival

The survival range for ARVC is broad. Sudden death due to ventricular arrhythmia can be a presenting symptom. Other individuals can be mildly affected, falling short of meeting diagnostic criteria. Overall, cardiac mortality and need for transplant is 5% or less.[2]

Test Information

Introduction

Testing for ARVC may include known familial mutation analysis, single gene sequence analysis, single gene deletion/duplication analysis, and/or multigene panel testing.

Known Familial Mutation Analysis

Analysis for known familial mutations is typically performed by Sanger sequencing, but if available, a targeted mutation panel that includes the familial mutation may be performed.

Known familial mutation analysis is performed when a causative mutation has been identified in a close relative of the individual requesting testing.

Sequence Analysis

Until recently, most sequencing tests used the Sanger sequencing methodology that was originally developed in the 1970s. Sanger sequencing is labor intensive and did not lend itself to high-throughput applications.

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more

efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. NGS may not perform as well as Sanger sequencing in some applications.

NGS tests vary in technical specifications (e.g., depth of coverage, extent of intron/exon boundary analysis, methodology of large deletion/duplication analysis).

Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

The efficiency of NGS has led to an increasing number of large, multigene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions.

Results may be obtained that cannot be adequately interpreted based on the current knowledge base. When a sequence variation is identified that has not been previously characterized or shown to cause the disorder in question, it is called a variant of uncertain significance (VUS). VUSs are relatively common findings when sequencing large amounts of DNA with NGS.

Under certain circumstances, technologies used in multigene testing may fail to identify mutations that might be identifiable through single-gene testing. If high clinical suspicion exists for a particular syndrome testing for that syndrome should be performed instead of a broad multigene panel.

Since genes can be easily added or removed from multigene tests over time by a given lab, medical records must document which genes were included in the specific multigene test used and in which labs they were performed.

Additionally, tests should be chosen to

- maximize the likelihood of identifying mutations in the genes of interest
- contribute to alterations in patient management
- minimize the chance of finding variants of uncertain clinical significance

ARVC Sequencing

ARVC multi-gene panels should include a minimum of 6 genes: DSC2, DSG2, DSP, JUP, PKP2, and TMEM43. PKP2 mutation is the most common cause of inherited ARVC. ARVC gene panels vary by laboratory and additional genes are included in some larger panels with limited diagnostic yield.[6-9]

Due to reported digenic inheritance (pathogenic mutations in two separate genes) in 4-47% of individuals, panel testing is strongly recommended for ARVC over sequential single gene testing.[2]

Multi-gene panels should be focused on the genes known to be associated with ARVC. No evidence has been found to suggest larger combined cardiac panels have a higher yield rate for ARVC patients.

Test yield has not been demonstrably higher when large scale testing is used versus disease specific panels.[1,6,8]

Predisposition testing for asymptomatic individuals by multi-gene panel testing is not recommended.[2]

Deletion/Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, MLPA, and NGS data analysis.

These assays detect gains and losses too large to be identified through sequencing technology, often single or multiple exons or whole genes.

Guidelines and Evidence

Introduction

This section includes relevant guidelines and evidence pertaining to ARVC testing.

American College of Cardiology

The American College of Cardiology (ACC, 2013) does not have an official position statement. However, they have published an article on the genetics of ARVC as a guide to physicians which included the following:[7]

- Testing for a known mutation in close relatives of an affected individual is beneficial.
- Periodic examination for persons who test positive for an ARVC genetic abnormality but do not have evidence of disease is recommended. Specifically, cardiac exam starting at 10 years of age every 2 years until age 20 and then every 5 years until age 60.
- Genetic counseling is recommended for all individuals with a genetically transmitted heart disease.

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2018) published a practice resource on genetic testing for cardiomyopathies. This

practice resource is an abbreviated version of the Heart Failure Society Guidelines above, on which ACMG collaborated. They stated:[10]

- "Recommendation 1. Genetic testing is recommended for patients with cardiomyopathy."
- "(a) Genetic testing is recommended for the most clearly affected family member."
- "(b) Cascade genetic testing of at-risk family members is recommended for pathogenic and likely pathogenic variants."
- "(c) In addition to routine newborn screening tests, specialized evaluation of infants with cardiomyopathy is recommended, and genetic testing should be considered."

European Heart Rhythm Association, Heart Rhythm Society, Asia Pacific Heart Rhythm Society, and Latin American Heart Rhythm Society

An expert consensus statement from the European Heart Rhythm Association, the Heart Rhythm Society, the Asia Pacific Heart Rhythm Society and the Latin American Heart Rhythm Society (EHRA/HRS/APHR/LAHRS, 2022) addressed the utility and appropriateness of genetic testing for inherited cardiovascular conditions.[11] The consensus statements were categorized as follows:

- Supported by strong observational evidence and authors' consensus
- Some evidence and general agreement favor the usefulness/ efficacy of a test
- There is evidence or general agreement not to recommend a test

Regarding the choice of genetic testing and variant interpretation:

- Genetic testing should occur with genetic counseling. [Supported by strong observational evidence and authors' consensus]
- If an individual has a clear phenotype, it is appropriate to analyze genes with definite/strong evidence support disease causation [Supported by strong observational evidence and authors' consensus] and may be appropriate to analyze genes with moderate evidence for disease causation. [Some evidence and general agreement favor the usefulness/ efficacy of a test]
- In some cases with a clear phenotype and negative genetic testing of genes with definite/strong evidence for disease causation, broader genetic testing may be considered. [Some evidence and general agreement favor the usefulness/ efficacy of a test]
- "Genetic testing for genes with (i) limited, (ii) disputed, or (iii) refuted evidence should not be performed in patients with a weak (non-definite) phenotype in the clinical setting." [There is evidence or general agreement not to recommend a test]

- "Variant interpretation in the clinical setting is greatly enhanced by the use of disease-specific, multi-disciplinary teams that could include clinical disease experts, clinical geneticists, or genetic counsellors and molecular geneticists." Standard guidelines for variant interpretation should be used. Variant interpretation "can be enhanced by gene-specific rule specifications tailored for the gene and disease under consideration. [Supported by strong observational evidence and authors' consensus]
- Variants of uncertain significance may be reclassified to likely pathogenic, pathogenic, likely benign or benign. [Some evidence and general agreement favor the usefulness/ efficacy of a test]
- When a likely pathogenic or pathogenic variant has been identified, genetic counseling should be offered. The inheritance pattern, penetrance, and associated risks can be discussed. Additionally, cascade testing for relatives can be facilitated. [Supported by strong observational evidence and authors' consensus]
- Some affected individuals may have had previous genetic testing that was not a comprehensive, such as prior to the use of next generation sequencing or with an incomplete testing panel. Repeat testing should be considered in these cases. [Supported by strong observational evidence and authors' consensus]

The statements for genetic testing encompassed all types of arrhythmogenic cardiomyopathy (ACM) and were not specific to ARVC.

- "Comprehensive genetic testing is recommended for all patients with consistent phenotypic features of ACM, including those cases diagnosed post-mortem, whatever familial context." [Supported by strong observational evidence and authors' consensus]
- "Genetic testing of first tier definitive disease-associated genes (currently PKP2, DSP, DSG2, DSC2, JUP, TMEM43, PLN, FLNC, DES, LMNA) is recommended." [Supported by strong observational evidence and authors' consensus]. Of note, this list includes genes for all types of ACM and not only ARVC.
- "Owing to the possibility of complex genotypes, in families with multiple affected members, the case with the more severe and/or earlier phenotype may be considered the 'genetic proband' and be tested first." [Some evidence and general agreement favor the usefulness/ efficacy of a test]
- "In patients with a borderline ACM phenotype, comprehensive genetic testing may be considered. The identification of a LP/P [likely pathogenic/pathogenic] genetic variant would be useful to confirm the diagnosis." [Some evidence and general agreement favor the usefulness/ efficacy of a test]

- **"Predictive genetic testing in related children is recommended in those aged >10–12 years." [Supported by strong observational evidence and authors' consensus]**
- **"Predictive genetic testing in related children aged below 10–12 years may be considered, especially where there is a family history of early-onset disease." [Some evidence and general agreement favor the usefulness/ efficacy of a test]**

European Society for Cardiology

The European Society for Cardiology (ESC, 2015) has the following guidelines for management of individuals with ARVC:[1]

- **"Targeted post-mortem genetic analysis of potentially disease causing genes should be considered in all sudden death victims in whom a specific inheritable channelopathy or cardiomyopathy is suspected."**
- **"Genetic screening of a large panel of genes should not be performed in SUDS or SADS relatives without clinical clues for a specific disease after clinical evaluation."**

Heart Failure Society of America

The Heart Failure Society of America (HFSA, 2018) stated:[12]

- **"Guideline 4: Genetic testing is recommended for patients with cardiomyopathy (Level of evidence A)"**
  - **"4a: Genetic testing is recommended for the most clearly affected family member."**
  - **"4b: Cascade genetic testing of at-risk family members if recommended for pathogenic and likely pathogenic variants."**
- **"Genetic testing is recommended to determine if a pathogenic variant can be identified to facilitate patient management and family screening."**
- **"Testing should ideally be initiated on the person in a family with the most definitive diagnosis and most severe manifestations. This approach would maximize the likelihood of obtaining diagnostic results and detecting whether multiple pathogenic variants may be present and contributing to variable disease expression or severity."**
- **"Molecular genetic testing for multiple genes with the use of a multigene panel is now the standard of practice for cardio-vascular genetic medicine. Furthermore, multigene panel genetic testing is recommended over a serial single-gene testing approach owing to the genetically heterogeneous nature of cardiomyopathy. Genetic testing and cascade screening have been shown to be cost-effective."**

- **"In ARVC, ICD placement for primary prevention in asymptomatic male carriers of a malignant pathogenic variant showed a significant effect on long-term clinical outcome."**

Criteria

Introduction

Requests for ARVC testing are reviewed using these criteria.

Known Familial Mutation Analysis

- **Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND**
- **Previous Genetic Testing:**
  - **No previous genetic testing that would detect the familial mutation, and**
  - **Known disease-causing familial mutation in ARVC gene identified in 1st or 2nd degree relative(s), AND**
- **Rendering laboratory is a qualified provider of service per the Health Plan policy**

Multi-Gene Panel Testing

- **Genetic counseling:**
  - **Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND**
- **Previous Genetic Testing:**
  - **No previous full sequencing of requested genes, and**
  - **No known mutation identified by previous analysis, AND**
- **Diagnostic Testing for Symptomatic Individuals:**
  - **Personal History**
    - **Confirmed diagnosis of ARVC by electrocardiogram, MRI, or angiogram meeting the task force criteria for at least possible ARVC (defined as having one major or two minor criteria), and**
    - **No evidence of other syndromes with cardiac findings such as Marfan Syndrome or Thoracic Aortic Aneurysms and Dissection (TAAD), in the individual or family, and**
    - **Non-genetic causes such as infection, toxin exposure, and metabolic/autoimmune disease have been ruled out, OR**

- **Personal & Family History Combination**
  - **A diagnosis of ARVC or possible ARVC with one or more 1st or 2nd degree relatives with a diagnosis of ARVC, or**
  - **A diagnosis of ARVC or possible ARVC with a suspicious family history including a 1st or 2nd degree relative with sudden adult death or young cardiac event, AND**
- **Documentation from ordering provider indicating how test results will be used to directly impact medical care for the individual (e.g. change in surveillance or treatment plan), AND**
- **Rendering laboratory is a qualified provider of service per the Health Plan policy**

Deletion/Duplication Analysis

- **Genetic Counseling:**
  - **Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND**
- **Previous Genetic Testing:**
  - **Member does not have a known mutation in an ARVC gene, and**
  - **No previous deletion/duplication analysis for ARVC genes, and**
  - **Member meets criteria for full sequence analysis of ARVC genes, AND**
- **Rendering laboratory is a qualified provider of service per the Health Plan policy**

Billing and Reimbursement Considerations

- **When multiple CPT codes are billed for components of a panel and there is a more appropriate CPT code representing the panel, eviCore will redirect to the panel code(s).**
- **If the laboratory will not accept redirection to a panel code, the medical necessity of each billed component procedure will be assessed independently.**
  - **In general, only a limited number of panel components that are most likely to explain the member's presentation will be reimbursable. The remaining panel components will not be reimbursable.**
  - **When the test is billed with multiple stacked codes, only the following genes may be considered for reimbursement:**
    - **DSC2**
    - **DSG2**

- DSP
- JUP
- PKP2
- TMEM43

References

Introduction

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