Genetic Testing for Diagnosis and Management of Hereditary Cardiomyopathies (including ARVD/C)

Description/Scope

This document addresses genetic testing for the hereditary cardiomyopathies which includes hypertrophic (HCM), dilated (DCM), restrictive (RCM), arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) and left ventricular noncompaction (LVNC).

Note: This document addresses genetic testing for hereditary cardiomyopathies only. For information about genetic testing for other hereditary cardiac conditions, see:

- GENE.00007 Cardiac Ion Channel Genetic Testing

Position Statement

Medically Necessary:

Genetic testing for hereditary hypertrophic cardiomyopathies (HCM) is considered medically necessary when all of the following criteria are met:

A. The individual to be tested has a first degree family member with a documented HCM and the first degree relative also has a genetic mutation with strong evidence for pathogenicity; and
B. The individual to be tested has been clinically screened (for example, with EKG, echocardiogram, or cardiac magnetic resonance imaging [MRI]) and does not have a diagnosis of HCM; and
C. Genetic counseling, which encompasses all of the following components, has been performed:
   1. Interpretation of family and medical histories to assess the probability of disease occurrence or recurrence; and
   2. Education about inheritance, genetic testing, disease management, prevention and resources; and
   3. Counseling to promote informed choices and adaptation to the risk or presence of a genetic condition; and
   4. Counseling for the psychological aspects of genetic testing.

Investigational and Not Medically Necessary:

Genetic testing for determining the diagnosis and for management of hereditary HCM is considered investigational and not medically necessary when the above criteria are not met.

Genetic testing for determining the diagnosis and for management of all other hereditary cardiomyopathies, including but not limited to, arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C), dilated, restrictive, and left ventricular noncompaction cardiomyopathies, is considered investigational and not medically necessary for all indications.

Rationale

Genetic testing has been proposed to determine an individual's predisposition to hypertrophic cardiomyopathy (HCM) among those persons considered to be at risk, due to confirmed HCM in a close family member. Familial HCM is the most common hereditary cardiac condition in the U.S. and is thought to be the most common cause of sudden cardiac death (SCD) in young athletes and others 35 years of age and younger. Developments in the field of genetic testing have led to identification of specific genetic mutations that are associated with high risk for HCM. Proponents of this testing suggest that identification of these mutations in at risk individuals may lead to improved clinical outcomes.

According to the HFSA practice guideline on genetic testing:

The available clinical genetics data for each of the cardiomyopathies varies greatly in content and quality, and thus, the quality and certainty of genetic counseling information is also variable. So too, the evidence that supports clinical genetic testing varies greatly. Although analytic validity (the ability of the test to detect a mutation) is attainable with current methods, evidence to support clinical validity (the ability of the test to detect the condition) remains quite limited for most cardiomyopathies, the exception being HCM. A separate measurement, clinical utility, defines the global risks and benefits of any test, asking the all-important question: how will the genetic information, whether positive or negative, affect clinical decision-making…Clinical utility remains to be defined for all genetic testing of cardiomyopathies (Hershberger, 2009).
This information was updated in 2011 in a Heart Failure Society of America/European Heart Rhythm Association (HRS/EHRA) Consensus Statement on the State of Genetic Testing for Channelopathies and Cardiomyopathies (Ackerman, 2011) which included the following guidance:

- A Class I recommendation ("is recommended") was applied for genetic testing in index cases with a sound clinical suspicion for the presence of a channelopathy or a cardiomyopathy when the positive predictive value of a genetic test is high (likelihood of positive result > 40% and signal/noise ratio > 10) AND/OR when the genetic test result provides either diagnostic or prognostic information, or when the genetic test result influences therapeutic choices;
- Screening of family members for the mutation identified in the proband of the family is recommended as a Class I when genetic testing leads to the adoption of therapy/protective measures/lifestyle adaptations;
- Conversely, the authors have assigned a Class IIa recommendation when results of genetic testing are not associated with the use of therapeutic or protective measures but the results may be useful for reproductive counseling or instances in which genetic testing is requested by the patient who wants to know his/her mutation status.

Regarding the strength of the evidence currently available for genetic testing, this HRS/EHRA Consensus Statement provided the following additional information:

Documents produced by other scientific societies have acknowledged the need to define the criteria used to rank the strength of recommendation for genetic diseases. The most obvious difference is that randomized and/or blinded studies do not exist. Instead, most of the available data are derived from registries that have followed patients and recorded outcome information…Contrary to common misperception, genetic tests are probabilistic tests, not deterministic tests. Many positive test results contain the index case’s and his/her family’s definitive disease-causing mutation, the proverbial pathogenic "smoking gun." However, many so-called "positive" test results are represented by less informative DNA variants currently annotated with the expression, "Variants of Uncertain Significance" (VUS). Only recently is the frequency of rare VUS among otherwise healthy volunteers across the exomes of various disease-causing genes being identified…Regardless of the disease in question or the specific genetic test pursued, treatment decisions should not rely solely on the patient's genetic test result but should be based on results from his/her comprehensive clinical evaluation.

Ackerman (HRS/EHRA Consensus Statement, 2011) also noted:

When using or considering the guidance from this document, it is important to remember that there are no absolutes governing many clinical situations. The final judgment regarding care of a particular patient must be made by the health care provider and the patient in light of all relevant circumstances (Ackerman, 2011).

In 2011, the American College of Cardiology Foundation and the American Heart Association (ACCF/AHA) Task Force on Practice Guidelines issued a Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy (Gersh, 2011) which included the following recommendations:

- Evaluation of familial inheritance and genetic counseling is recommended as part of the assessment of patients with HCM; (Class I; Level of Evidence: B)
- Screening (clinical, with or without genetic testing) is recommended in first-degree relatives of patients with HCM; (Class I; Level of Evidence: B)
- Genetic testing for HCM and other genetic causes of unexplained cardiac hypertrophy is recommended in patients with an atypical clinical presentation of HCM or when another genetic condition is suspected to be the cause; (Class I; Level of Evidence: B)
- Genetic testing is reasonable in the index patient to facilitate the identification of first-degree family members at risk for developing HCM. (Class IIa; Level of Evidence: B)

According to a recent review paper on the current knowledge base for the genetics of HCM testing (Maron, 2012), the following genetic mutations have strong evidence for pathogenicity in HCM:

**Thick filament:**
- β-myosin heavy chain -- MYH7
- Regulatory myosin light chain -- MYL2
- Essential myosin light chain -- MYL3

**Thin filament:**
- Cardiac troponin T -- TNNT2
- Cardiac troponin I -- TNNI3
- Cardiac troponin C -- TNNC1
- α-tropomyosin -- TPM1
- α-cardiac actin -- ACTC

**Intermediate filament:**
- Cardiac myosin-binding protein C -- MYBPC3

https://www.anthem.com/medicalpolicies/policies/mp_pw_c132947.htm

2/8
natural_text
Sudden cardiac death (also called sudden death [SCD]): This term refers to death resulting from an abrupt loss of heart function (cardiac arrest).

**Coding**

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage or these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met for HCM:

**CPT**

- **81403**
  - Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons) [when specified as the following]:
    - *PLN (phospholamban)* (eg, dilated cardiomyopathy, hypertrophic cardiomyopathy), full gene sequence

- **81405**
  - Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) [when specified as the following]:
    - *ACTC1 (actin, alpha, cardiac muscle 1)* (eg, familial hypertrophic cardiomyopathy), full gene sequence
    - *MYL2 (myosin, light chain 2, regulatory, cardiac, slow)* (eg, familial hypertrophic cardiomyopathy), full gene sequence
    - *MYL3 (myosin, light chain 3, alkali, ventricular, skeletal, slow)* (eg, familial hypertrophic cardiomyopathy), full gene sequence
    - *TNNC1 (troponin C type 1 [slow])* (eg, hypertrophic cardiomyopathy or dilated cardiomyopathy), full gene sequence
    - *TNNI3 (troponin I, type 3 [cardiac])* (eg, familial hypertrophic cardiomyopathy), full gene sequence
    - *TPM1 (tropomyosin 1 [alpha])* (eg, familial hypertrophic cardiomyopathy), full gene sequence

- **81406**
  - Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) [when specified as the following]:
    - *PRKAG2 (protein kinase, AMP-activated, gamma 2 non-catalytic subunit)* (eg, familial hypertrophic cardiomyopathy with Wolff-Parkinson-White syndrome, lethal congenital glycogen storage disease of heart), full gene sequence
    - *TNNT2 (troponin T, type 2 [cardiac])* (eg, familial hypertrophic cardiomyopathy), full gene sequence

- **81407**
  - Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform) [when specified as the following]:
    - *MYBPC3 (myosin binding protein C, cardiac)* (eg, familial hypertrophic cardiomyopathy), full gene sequence
    - *MYH7 (myosin, heavy chain 7, cardiac muscle, beta)* (eg, familial hypertrophic cardiomyopathy, Liang distal myopathy), full gene sequence

- **81479**
  - Unlisted molecular pathology procedure [when specified as a gene panel for hereditary hypertrophic cardiomyopathy]

**HCPCS**

- **S3866**
  - Genetic analysis for a specific gene mutation for hypertrophic cardiomyopathy (HCM) in an individual with a known HCM mutation in the family

**ICD-10 Diagnosis**

- **I42.0-I42.9**
  - Cardiomyopathy [when specified for hereditary hypertrophic cardiomyopathy]

- **Z82.41-Z82.49**
  - Family history of ischemic heart disease and other diseases of the circulatory system [when specified as hereditary hypertrophic cardiomyopathy]

https://www.anthem.com/medicalpolicies/policies/mp_pw_c132947.htm
When services are Investigational and Not Medically Necessary:
For the procedure codes listed above, when criteria are not met for hereditary hypertrophic cardiomyopathy.

When services are Investigational and Not Medically Necessary:

CPT
81405
Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons), regionally targeted cytogenomic array analysis [when specified as the following]:

- ANKRD1 (*ankyrin repeat domain 1*) (eg, dilated cardiomyopathy), full gene sequence

81406
Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) [when specified as the following]:

- DSC2 (*desmocollin*) (eg, arrhythmogenic right ventricular dysplasia/ cardiomyopathy 11), full gene sequence
- DSG2 (*desmoglein 2*) (eg, arrhythmogenic right ventricular dysplasia/ cardiomyopathy 10), full gene sequence
- DSP (*desmoplakin*) (eg, arrhythmogenic right ventricular dysplasia/cardiomyopathy 8), full gene sequence
- JUP (*junction plakoglobin*) (eg, arrhythmogenic right ventricular dysplasia/ cardiomyopathy 11), full gene sequence
- LDB3 (*LIM domain binding 3*) (eg, familial dilated cardiomyopathy, myofibrillar myopathy), full gene sequence
- PKP2 (*plakophilin 2*) (eg, arrhythmogenic right ventricular dysplasia/ cardiomyopathy 9), full gene sequence
- TMEM43 (*transmembrane protein 43*) (eg, arrhythmogenic right ventricular cardiomyopathy), full gene sequence

81407
Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform) [when specified as the following]:

- MYH6 (*myosin, heavy chain 6, cardiac muscle, alpha*) (eg, familial dilated cardiomyopathy), full gene sequence
- SCN5A (*sodium channel, voltage-gated, type V, alpha subunit*) (eg, familial dilated cardiomyopathy), full gene sequence

81408
Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis) [when specified as the following]:

- RYR2 (*ryanodine receptor 2 [cardiac]*) (eg, catecholaminergic polymorphic ventricular tachycardia, arrhythmogenic right ventricular dysplasia), full gene sequence or targeted sequence analysis of >50 exons

81479
Unlisted molecular pathology procedure [when specified as a gene panel for other than hereditary hypertrophic cardiomyopathy, such as ARVC test, DCM test, CD-DCM test]

ICD-10 Diagnosis
I42.0-I42.9
Cardiomyopathy [when specified for cardiomyopathy other than hereditary HCM]

282.41-282.49
Family history of ischemic heart disease and other diseases of the circulatory system [when specified as cardiomyopathy other than hereditary HCM]

When services are also Investigational and Not Medically Necessary:

CPT
81439
Inherited cardiomyopathy (eg, hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy) genomic sequence analysis panel, must include sequencing of at least 5 genes, including DSG2, MYBPC3, MYH7, PKP2 and TTN [Note: code effective 01/01/2017]

HCPCS
S3865
Comprehensive gene sequence analysis for hypertrophic cardiomyopathy

ICD-10 Diagnosis
All diagnoses
Peer Reviewed Publications:


Government Agency, Medical Society, and Other Authoritative Publications:


Websites for Additional Information

Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C)
Cardiomyopathy, Hypertrophic (HCM)
Familial Dilated Cardiomyopathy (FDC)
Familial Hypertrophic Cardiomyopathy (FHCM)
FAMILION
Genetic Testing

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

### Document History

<table>
<thead>
<tr>
<th>Status</th>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>Revised</td>
<td>05/04/2017</td>
<td>Medical Policy &amp; Technology Assessment Committee (MPTAC) review. Updated the medically necessary statements to include criteria for genetic counseling. Updated Background/Overview, Definitions, References and History sections.</td>
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