Clinical Policy: Genetic Testing for Catecholaminergic Polymorphic Ventricular Tachycardia

Reference Number: HNCA.CP.MP.493
Effective Date: 10/09
Last Review Date: 06/19

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Catecholaminergic polymorphic ventricular tachycardia (CPVT), also known as familial CPVT, is a rare disorder characterized by episodic syncope occurring during exercise or acute emotion in individuals without structural cardiac abnormalities and an unremarkable resting electrocardiagram (ECG).

Policy/Criteria
I. It is the policy of Health Net of California that genetic testing for CPVT is **medically necessary** for any of the following indications:
- A. To confirm the diagnosis of CPVT in individuals who demonstrate exercise induced ventricular arrhythmias in the presence of an unremarkable ECG and absence of cardiac abnormalities
- B. Individuals with a positive family history of sudden death in children or young adults and based on clinical evaluation (eg. history and physical, resting ECG, ECG and exercise stress testing), CPVT is suspected
- C. Predictive testing for at-risk symptomatic family members when there is a positive genetic test in a first degree relative (i.e., individual's parents, full siblings, and children)

Background
CPVT typically begins in childhood or adolescence, although cases have been reported with initial presentation in the fourth decade of life. Affected individuals may have a family history of juvenile sudden death or stress-induced syncope. CPVT may also present sporadically as a de novo mutation in individuals with no family history. Affected patients typically present with life threatening ventricular tachycardia or ventricular fibrillation occurring during emotional or physical stress, with syncope often being the first manifestation of the disease.

The two genes with mutations that have been identified with CPVT are the cardiac ryanodine receptor gene (which may have the p.G357S RyR2 mutation), an autosomal dominant form and the calsequestrin 2 gene, autosomal recessive. Both mutations appear to act by inducing diastolic calcium release from the sarcoplasmic reticulum. The resulting intracellular calcium overload leads to delayed afterdepolarizations and triggered activity, which can induce ventricular tachycardia and fibrillation. It should be noted that mutations in these two genes have been recognized in only 60% of patients with CPVT, implying that other genes may play a role. [2]

American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology

Beta blockers are recommended as first-line treatment in all affected individuals, (class I indication) and the use of the implantable cardioverter-defibrillator is recommended for higher-risk subgroups. The guidelines note that genetic analysis may help identify silent carriers of CPVT related mutations. Once identified silent carriers may be treated with beta blockers to reduce the risk of cardiac events and may receive appropriate genetic counseling to assess the risk of transmitting the disease to offspring. [10]

Most of the data available for inherited arrhythmogenic diseases such as Long QT syndrome, Brugada syndrome and CPVT, are derived from large registries that have followed patients over time, recording outcome information. They note that no randomized studies are available, and most likely they will never be conducted in these uncommon conditions. [10]

A study was completed to try to identify the genetic cause of CPVT in specific families, to preventively treat and clinically characterize the mutation-positive individuals, and to functionally characterize the pathogenic mechanisms of the mutation. Genetic testing was performed for 1404 relatives. Functional studies showed that the G357S mutation increased caffeine sensitivity and store overload-induced calcium release activity under conditions that mimic catecholaminergic stress. The study supports the use of genetic testing to identify individuals at risk of SCD to undertake prophylactic interventions. [9]

A number of other studies also note the importance of genetic testing for the early diagnosis of asymptomatic carriers, the prevention of sudden death, as well as to initiate appropriate prophylactic interventions. [5689]

Coding Implications

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CPT® Codes	Description
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) [i.e.,.CASQ2 (Calsequestrin 2, cardiac muscle), e.g., catecholaminergic polymorphic ventricular tachycardia] full gene sequence

CPT® Codes	Description
81408	Molecular Pathology Procedure, Level 9, e.g., analysis of >50 exons in a single gene by DNA sequence analysis [i.e., RyR2 (ryanodine receptor 2 (cardiac) e.g. catecholaminergic polymorphic Ventricular tachycardia , arrhythmogenic right ventricular dysplasia, full gene sequence of targeted sequence analysis >50 exons
81413	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); genomic sequence analysis panel, must include sequencing of at least 10 genes, including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A
81414	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); duplication/deletion gene analysis panel, must include analysis of at least 2 genes, including KCNH2 and KCNQ1

HCPCS Codes	Description
N/A	

ICD-10-CM Diagnosis Codes that Support Coverage Criteria

ICD-10-CM Code	Description
I47.2	Ventricular tachycardia
I49.041	Ventricular fibrillation
R55	Syncope and collapse
Z13.6	Encounter for screening for cardiovascular disorders
Z13.79	Encounter for other screening for genetic and chromosomal anomalies
Z82.41	Family history of sudden cardiac death

Reviews, Revisions, and Approvals	Date	Approval Date
Policy Adopted from Health Net NMP # 493 Genetic Testing for Catecholaminergic Polymorphic Ventricular Tachycardia	06/17	
Update and no changes	6/18	

References

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3. European Heart Rhythm Association, Heart Rhythm Society, ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. A report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines. Am Coll Cardiol 2006 Sep 5; 48(5): e247-346.
4. Hayes. Genetic Test Evaluation Overview. Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) for Ventricular Tachycardia. March 17, 2014. Archived January 8, 2016.
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6. Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA and APHRS in May 2013 and by ACCF, AHA, PACES and AEPC in June 2013 Heart Rhythm 2013; 10:1932.
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8. Tan HL, Hofman N, van Langen, IM et al. Sudden unexplained death: heritability and diagnostic yield of cardiological and genetic examination in surviving relatives. Circulation. 2005 Jul 12; 112(2): 207-13.
9. Wangüemert F, Bosch Calero C, Pérez C, et al. Clinical and molecular characterization of a cardiac ryanodine receptor founder mutation causing catecholaminergic polymorphic ventricular tachycardia. Heart Rhythm. 2015 Jul;12(7):1636-43. doi: 10.1016/j.hrthm.2015.03.033. Epub 2015 Mar 23.
10. Zipes DP, Camm AJ, Borggrefe M, et al.; American College of Cardiology/American Heart Association Task Force; European Society of Cardiology Committee for Practice Guidelines; European Heart Rhythm Association; Heart Rhythm Society. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*. 2006;114(10):e385-e484.

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program

approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare members, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.