Geisinger

Geisinger Health Plan Policies and Procedure Manual

Policy: MP304

Section: Medical Benefit Policy

Subject: Genetic Testing for Inherited Cardiomyopathies and Channelopathies

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I. Policy: Genetic Testing for Inherited Cardiomyopathies and Channelopathies

II. Purpose/Objective:

To provide a policy of coverage regarding Genetic Testing for Inherited Cardiomyopathies and Channelopathies

III. Responsibility:

A. Medical Directors
B. Medical Management

IV. Required Definitions

1. Attachment – a supporting document that is developed and maintained by the policy writer or department requiring/authoring the policy.
2. Exhibit – a supporting document developed and maintained in a department other than the department requiring/authoring the policy.
3. Devised – the date the policy was implemented.
4. Revised – the date of every revision to the policy, including typographical and grammatical changes.
5. Reviewed – the date documenting the annual review if the policy has no revisions necessary.

V. Additional Definitions

Medical Necessity or Medically Necessary means Covered Services rendered by a Health Care Provider that the Plan determines are:

a. appropriate for the symptoms and diagnosis or treatment of the Member's condition, illness, disease or injury;
b. provided for the diagnosis, and the direct care and treatment of the Member's condition, illness disease or injury;
c. in accordance with current standards of good medical treatment practiced by the general medical community.
d. not primarily for the convenience of the Member, or the Member's Health Care Provider; and
e. the most appropriate source or level of service that can safely be provided to the Member. When applied to hospitalization, this further means that the Member requires acute care as an inpatient due to the nature of the services rendered or the Member's condition, and the Member cannot receive safe or adequate care as an outpatient.

Medicaid Business Segment

Medical Necessity shall mean a service or benefit that is compensable under the Medical Assistance Program and if it meets any one of the following standards:

(i) The service or benefit will, or is reasonably expected to, prevent the onset of an illness, condition or disability.
(ii) The service or benefit will, or is reasonably expected to, reduce or ameliorate the physical, mental or development effects of an illness, condition, injury or disability.
(iii) The service or benefit will assist the Member to achieve or maintain maximum functional capacity in performing daily activities, taking into account both the functional capacity of the Member and those functional capacities that are appropriate for members of the same age.

DESCRIPTION: Cardiomyopathies are diseases of the heart muscle**.** Cardiac channelopathies are disorders involving cardiac cells membranes that allow passage of specific ions. These pathways regulate the flow of ions through the cells and are necessary to conduct electrical impulses across the heart. Cardiac channelopathies include long QT syndrome (LQTS), Brugada syndrome (BrS) (also referred to as sudden unexpected nocturnal death syndrome), short QT syndrome (SQTS) and Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT). Cardiac channelopathies are characterized by delayed repolarization of the myocardium and QT interval alteration, resulting in increased risk for syncope, seizures, and sudden cardiac death (SCD) in the setting of a structurally normal heart and otherwise healthy individual.

INDICATIONS: When ordered by a cardiologist/electrophysiologist, medical geneticist, or board-certified and licensed (where required) genetic counselor, the following tests are considered to be medically necessary:

Long QT Syndrome

Genetic testing in patients with suspected congenital long QT syndrome (LQTS) may be considered medically necessary for the following indications:

Individuals who do not meet the clinical criteria for LQTS (i.e., Schwartz score* less than 4), but who have any of the following:

- a first, second, or third-degree relative with a known LQTS mutation; or
- a first, second, or third-degree relative diagnosed with LQTS by clinical means but in whom the genetic status is unavailable; or
- signs and/or symptoms indicating a moderate-to-high pretest probability (i.e. Schwartz score of 2-3) of LQTS.

Short QT Syndrome

Genetic testing in patients with suspected congenital long QT syndrome (LQTS) may be considered medically necessary for the following indications:

- members with signs and/or symptoms of SQTS, but a definitive diagnosis cannot be made without genetic testing; or
- members who do not meet the clinical criteria for SQTS but who have a first, second, or third-degree relative with a known LQTS mutation

Catecholaminergic Polymorphic Ventricular Tachycardia

Genetic testing for catecholaminergic polymorphic ventricular tachycardia (CPVT) may be considered medically necessary for members who do not meet the clinical criteria for CPVT but who have:

- a first, second, or third-degree relative with a known CPVT mutation; or
- a first, second, or third-degree relative diagnosed with CPVT by clinical means but in whom the genetic status is unavailable; or
- signs and/or symptoms indicate a moderate-to-high pretest probability of CPVT

Brugada Syndrome

Genetic testing for Brugada syndrome (BrS) is considered medically necessary when documentation in the medical record indicates that all of the following criteria are met:

- The member has a type 1 Brugada ECG pattern that appears spontaneously or after the administration of an antiarrhythmic drug; or
- The member has one of the following:
    - A first or second- degree relative with a known BrS mutation; or
    - A first or second-degree relative with sudden death due to BrS; or
    - For the purposes of identifying a BrS mutation that can be used for family-specific screening in at-risk blood relatives.

Left Ventricular Noncompaction

Genetic testing for left ventricular noncompaction (LVNC) is considered medically necessary when:

- signs and/or symptoms consistent with LVNC are present, but a definitive diagnosis cannot be made without genetic testing; or
- a first, second, or third-degree relative has a known LVNC mutation.

Hypertrophic Cardiomyopathy

Genetic testing for hypertrophic cardiomyopathy (HCM) is considered medically necessary when:

- members are at risk for development of HCM due to a first-degree relative with established HCM and a known pathogenic gene mutation is present.

Dilated Cardiomyopathy

Genetic testing for dilated cardiomyopathy is considered medically necessary for members who:

- have dilated cardiomyopathy and significant cardiac conduction disease (i.e. first-, second, or third-degree heart block); or
- have one or more family members who experienced sudden cardiac death or developed unexplained heart failure before age 60.

Genetic testing for a known familial mutation associated with dilated cardiomyopathy is considered medically necessary in asymptomatic first, second, or third-degree relatives of a proband.

Restrictive Cardiomyopathy

Genetic testing for a known familial mutation associated with restrictive cardiomyopathy (RCM) is considered medically necessary in asymptomatic first, second, or third-degree relative of a proband.

Right Ventricular Cardiomyopathy

Genetic testing for arrhythmogenic right ventricular cardiomyopathy (ARVC) is considered medically necessary:

- When signs and/or symptoms consistent with ARVC are present, but a definitive diagnosis cannot be made without genetic testing; or
- Member has a first, second, or third-degree relative with a known ARVC mutation.

*Swartz Score Calculator for Clinical Diagnosis of Long QT Syndrome

Findings			Points
ECG [1]	QTc [2]	≥480 ms	3
		=460-479 ms	2
		=450-459 ms (in males)	1
		≥480 ms during 4th minute of recovery from exercise stress test	1
	Torsade de pointes		2
	T wave alternans		1
	Notched T wave in 3 leads		1
	Low heart rate for age		0.5
Clinical history	Syncope [3]	With stress	2
		Without stress	1
Family history	Family member(s) with definite LQTS		1
	Unexplained sudden cardiac death at age <30 years in immediate family		0.5
Total score			

Adapted from: Schwartz PJ, Crotti L. QTc behavior during exercise and genetic testing for the long-QT syndrome. Circulation. 2011;124:2181–4

Scoring:

- ≤1.0 point = low probability of LQTS
- 1.5-3.0 points = intermediate probability of LQTS
- ≥3.5 points = high probability of LQTS

EXCLUSIONS:
Genetic testing for inherited cardiomyopathies and channelopathies not meeting the criteria described above is considered to be experimental, investigational or unproven and therefore NOT COVERED. There is insufficient evidence in the published, peer-reviewed medical literature to support the use of this protesting outside of the indications listed above.

CODING ASSOCIATED WITH:
The coding listed in this document may not represent the comprehensive range of codes that may be associated with this service.

81280 Long QT Syndrome gene analysis (eg, KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1, and ANK2); full sequence analysis
81281 Long QT Syndrome gene analysis (eg, KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1, and ANK2); known familial sequence variant
81282 Long QT Syndrome gene analysis (eg, KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1, and ANK2); duplication / deletion variants
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)
81439 Hereditary cardiomyopathy (eg, hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy), genomic sequence analysis panel, must include sequencing of at least 5 cardiomyopathy-related genes
0231U CACNA1A (calcium voltage-gated channel subunit alpha 1A) (eg, spinocerebellar ataxia), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) gene expansions, mobile element insertions, and variants in non-uniquely mappable regions
0237U Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia), genomic sequence analysis panel including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions

LINE OF BUSINESS:
Eligibility and contract specific benefit limitations and/or exclusions will apply. Coverage statements found in the line of business specific benefit document will supercede this policy.

REFERENCES:

Kapplinger JD, Tester DJ, Alders M, et al. An international compendium of mutations in the SCN5A-encoded cardiac sodium channel in patients referred for Brugada syndrome genetic testing. Heart Rhythm. 2010;7(1):33-46.

Probst V, Veltmann C, Eckardt L, et al. Long-term prognosis of patients diagnosed with Brugada syndrome: results from the FINGER Brugada Syndrome Registry. Circulation. 2010;121(5):635-643

Priori SG, Napolitano C, Gasparini M, et al. Natural history of Brugada syndrome: insights for risk stratification and management. Circulation. 2002;105(11):1342-1347

Bai R, Napolitano C, Bloise R, Monteforte N, Priori SG. Yield of genetic screening in inherited cardiac channelopathies: how to prioritize access to genetic testing. Circ Arrhythm Electrophysiol. 2009;2(1):6-15

Sacher F, Probst V, Iesaka Y, et al. Outcome after implantation of a cardioverter-defibrillator in patients with Brugada syndrome: a multicenter study. Circulation. 2006;114(22):2317-2324

Sinner MF, Pfeufer A, Akyol M, et al. The non-synonymous coding IKr-channel variant KCNH2-K897T is associated with atrial fibrillation: results from a systematic candidate gene-based analysis of KCNH2 (HERG). Eur Heart J. 2008;29(7):907-914.

Goldenberg I, Moss AJ, Bradley J, et al. Long-QT syndrome after age 40. Circulation. 2008;117(17):2192-2201

Sauer AJ, Moss AJ, McNitt S, et al. Long QT syndrome in adults. J Am Coll Cardiol. 2007;49(3):329-337.

Moss AJ, Shimizu W, Wilde AA, et al. Clinical aspects of type-1 long-QT syndrome by location, coding type, and biophysical function of mutations involving the KCNQ1 gene. Circulation. 2007;115(19):2481-2489

Phillips KA, Ackerman MJ, Sakowski J, Berul CI. Cost-effectiveness analysis of genetic testing for familial long QT syndrome in symptomatic index cases. Heart Rhythm. 2005;2(12):1294-1300

Postma AV, Denjoy I, Kamblock J, et al. Catecholaminergic polymorphic ventricular tachycardia: RYR2 mutations, bradycardia, and follow up of the patients. J Med Genet. 2005;42(11):863-870.

Priori SG, Napolitano C, Memmi M, et al. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. Circulation. 2002;106(1):69-74.

Medeiros-Domingo A, Bhuiyan ZA, Tester DJ, et al. The RYR2-encoded ryanodine receptor/calcium release channel in patients diagnosed previously with either catecholaminergic polymorphic ventricular tachycardia or genotype negative, exercise-induced long QT syndrome: a comprehensive open reading frame mutational analysis. J Am Coll Cardiol. 2009;54(22):2065-2074.

di Barletta MR, Viatchenko-Karpinski S, Nori A, et al. Clinical phenotype and functional characterization of CASQ2 mutations associated with catecholaminergic polymorphic ventricular tachycardia. Circulation. 2006;114(10):1012-1019.

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.

Tester DJ, Will ML, Haglund CM, Ackerman MJ. Compendium of cardiac channel mutations in 541 consecutive unrelated patients referred for long QT syndrome genetic testing. Heart Rhythm. 2005;2(5):507-517.

Tester DJ, Salisbury BA, Carr JL, et al. The effect of mutation class on QTC in unrelated patients referred for the FamilionTM genetic test for long QT syndrome. Presented at: Heart Rhythm Society 28th Annual Scientific Sessions; May 9-12, 2007; Colorado, AZ. Abstract AB28-2. Heart Rhythm Society. Scientific Sessions. Past Meetings. Heart Rhythm 2007. Abstracts. Search: author (requires registration). Available at: http://www.abstracts2view.com/hrs07/sessionindex.php.

Tester DJ, Salisbury BA, Carr JL, et al. Clinical phenotype and the yield of the FamilionTM genetic test for congenital long QT syndrome. Presented at: Heart Rhythm Society 28th Annual Scientific Sessions; May 9-12, 2007; Colorado, AZ. Abstract AB10-3. Heart Rhythm Society. Scientific Sessions. Past Meetings. Heart Rhythm 2007. Abstracts. Search: author (requires registration). Available at: http://www.abstracts2view.com/hrs07/sessionindex.php.

Phillips KA, Ackerman MJ, Sakowski J, Berul CI. Cost-effectiveness analysis of genetic testing for familial long QT syndrome in symptomatic index cases. Heart Rhythm. 2005;2(12):1294-1300.

Kumar, S, Peters, S, Thompson, T, Morgan, et al. Familial cardiological and targeted genetic evaluation: low yield in sudden unexplained death and high yield in unexplained cardiac arrest syndromes. Heart Rhythm. 2013;10(11):1653-1660.

Schwartz PJ, Crotti L. QTc behavior during exercise and genetic testing for the long-QT syndrome. Circulation. 2011;124:2181–4

Arking, DE, Junttila, MJ, Goyette, P, et al. Identification of a sudden cardiac death susceptibility locus at 2q24.2 through genome-wide association in European ancestry individuals. PLoS Genet. 2011;7(6):e1002158.

Magi, S., Lariccia, V., Maiolino, M., Amoroso, S., & Gratteri, S. Sudden cardiac death: focus on the genetics of channelopathies and cardiomyopathies. J Biomed Sci, 2017; 24.

Kalia, S. S., Adelman, K., Bale, S. J., Chung, W. K., Eng, C., Evans, J. P. et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genetics In Medicine, 2016;19, 249.

Hershberger, R. E., Givertz, M. M., Ho, C. Y., Judge, D. P., Kantor, P. F., McBride, K. L. et al. Genetic evaluation of cardiomyopathy: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2018 doi:10.1038/s41436-018-0039-z

van Lint, F. H. M., Mook, O. R. F., Alders, M., Bikker, H., Lekanne Dit Deprez, R. H., & Christiaans, I. Large next-generation sequencing gene panels in genetic heart disease: yield of pathogenic variants and variants of unknown significance. Neth Heart J, 2019;27(6), 304-309.

Adler A, Novelli V, Amin AS, Abiusi E, Care M, Nannenberg EA, et al. an international, multicentered, evidence-based reappraisal of genes reported to cause congenital long QT syndrome. Circulation. 2020 Feb 11;141(6):418-428

This policy will be revised as necessary and reviewed no less than annually.

Devised: 7/21

Revised:

Reviewed: