Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
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Plan: Keystone First Community Health Choices	**Submission Date**: 10/1/2023
Policy Number: ccp.1252	**Effective Date:** 10/2016 **Revision Date:** September 1, 2023
Policy Name: Genetic testing for hereditary cardiomyopathy	

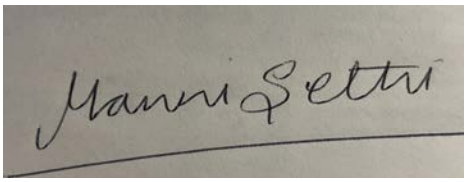
Type of Submission – Check all that apply:

New Policy
X Revised Policy*
Annual Review – No Revisions
Statewide PDL

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any clarifying information for the policy below:

See tracked changes below.

Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	**Signature of Authorized Individual:** 

Keystone First
Community HealthChoices

Genetic testing for hereditary cardiomyopathy

Clinical Policy ID: CCP.1252

Recent review date: 9/2023

Next review date: 1/2025

Policy contains: Genetic testing, hereditary cardiomyopathy, hypertrophic cardiomyopathy, sudden cardiac death.

Keystone First Community HealthChoices has developed clinical policies to assist with making coverage determinations. Keystone First Community HealthChoices' clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Keystone First Community HealthChoices when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Keystone First Community HealthChoices' clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Keystone First Community HealthChoices' clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First Community HealthChoices will update its clinical policies as necessary. Keystone First Community HealthChoices' clinical policies are not guarantees of payment..

Coverage policy

Genetic testing for hereditary cardiomyopathy susceptibility is clinically proven and, therefore, may be medically necessary for any of the following indications (Al-Khatib, 2018; Hershberger, 2018a, 2018b):

- Molecular confirmation of a clinical diagnosis in symptomatic patients.
- Molecular confirmation of anatomical abnormalities on imaging studies suggestive of hereditary cardiomyopathy.
- Risk assessment of asymptomatic first-degree family members of a proband with cardiomyopathy and/or arrhythmia.
- Differentiation of hereditary cardiomyopathy and/or arrhythmia from acquired (non-genetic) cardiomyopathy and/or arrhythmia.
- Recurrence risk calculation.

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

- Primary care and specialty care evaluation and diagnosis.
- Laboratory examination.

- Radiologic examination.

Background

Cardiomyopathy is disease that can stretch (dilate), thicken (hypertrophy), or stiffen (restrict) the heart muscle, which may lead to heart failure. In many cases, cardiomyopathy is the result of a disease sequelae or specific physiologic disorder (e.g., sarcoidosis, alcoholism). In other cases, it may result from genetic mutations (Bonaventura, 2021). A genetic cause can be identified in 30% of patients with non-compaction cardiomyopathy with clinical features ranging from asymptomatic cardiomyopathy to heart failure with major adverse cardiac events (van Waning, 2019).

The three most common forms of cardiomyopathy are hypertrophic, dilated, and arrhythmic right ventricular dysplasia. Hypertrophic cardiomyopathy is a common inherited heart condition defined as left or biventricular dilation and systolic malfunction that is unable to be explained by abnormal filling or coronary artery disease. It has an estimated prevalence of one in 250 people and is familial in 20-30% of individuals. In most cases it is thought to be a Mendelian type, a mainly autosomal dominant type of inherited disease, but many variants with small effect sizes are thought to contribute to inheritability reacting to environmental factors (Tayal, 2021).

Dilated cardiomyopathy may arise as a primary genetic disorder or as a secondary manifestation of other cardiovascular or systemic conditions (Burke, 2016). It is relatively common in clinical practice, occurring in one in 250 individuals (Hershberger, 2013). Altered myocardial calcium homeostasis is a common feature in genetic and acquired forms of dilated cardiomyopathy and can impact cardiac physiology by causing irregularities in contractile force, signaling pathways, and gene transcription. Inherited dilated cardiomyopathy occurs in 30% to 50% of cases of the disease, with autosomal dominant inheritance being the most common means of transmission (Towbin, 2014).

Arrhythmic right ventricular dysplasia is a familial disease in around 50% of cases and is usually transmitted in an autosomal dominant fashion. It is characterized pathologically as a progressive fibro-fatty replacement of the right ventricular musculature. The first gene associated with this condition, arrhythmic right ventricular dysplasia 1, coding for a desmosome protein, was discovered in 1994. Hereditary conditions known to cause this restrictive cardiomyopathy include hemochromatosis, glycogen storage diseases, Fabry disease, inherited cardiomyopathy Gaucher disease, and Hurler syndrome (Saugner, 2014). Factors associated with risk of arrhythmic events in this population include male gender, presyncope, left ventricular dysfunction, T-wave inversions in inferior leads, proband status, late potentials, syncope, inducibility at electrophysiological study, right ventricular dysfunction, epsilon waves, and premature ventricular contractions greater than 1000 per 24 hours (Bazoukis, 2019).

Recent advances in cardiovascular genetic testing have transformed the lives of families with inherited cardiomyopathies. While genetic testing by Sanger sequencing for individual genes may be performed, multi-gene panels employing next-generation sequencing have grown in popularity. The composition of gene panels varies, and specific gene panels for well-defined phenotypes are available. Cardiologists must weigh the benefits of expanded testing with likelihood of identifying variants of uncertain significance. The main benefits of genetic testing in inherited cardiomyopathies, along with genetic counselling, are identifying undiagnosed family members and prognosis (Vogiatzi, 2022).

Findings

In general, guidelines recommend genetic testing for known or suspected inherited cardiomyopathy when the results may change management (of the patient or family members), and when it is cost-effective. Genetic testing is most beneficial at the time a new cardiomyopathy diagnosis is made. Because inherited cardiomyopathies can

be genetically heterogenous and have overlapping phenotypic features, multigene panel genetic testing is recommended over a serial single-gene testing and should be based on the specifics of the patient's medical history, physical exam findings, and family history.

The American Heart Association, American College of Cardiology, and Heart Rhythm Society issued a guideline on management of patients with ventricular arrhythmias and preventing sudden cardiac death. Included in the guideline were genetic testing and counselling indications for patients with cardiomyopathy such as risk stratification for sudden cardiac arrhythmia or sudden cardiac death, or detection of a heritable disease that may clarify prognosis or diagnosis, and cascade screening of relatives. (Al-Khatib, 2018).

A combined practice guideline issued by the American College of Medical Genetics and Genomics and the Heart Failure Society of America asserted the necessity for genetic evaluation for persons diagnosed with cardiomyopathy, and also includes recommended clinical approaches after secondary findings from cardiomyopathy genes. The recommendations add that patients who undergo genetic testing should receive counseling from an expert (Hershberger, 2018).

The American College of Cardiology Foundation and American Heart Association recommended that genetic testing for hypertrophic cardiomyopathy be accompanied by genetic counseling from a trained professional, and that in the case of positive results, first-degree relatives be screened for the genetic evidence of the disorder, as they are considered risk factors for death from hypertrophic cardiomyopathy (Ommen, 2020). The European Society of Cardiology also maintains a set of guidelines for diagnosing and managing hereditary cardiomyopathy (Elliott, 2014).

Conclusive medical evidence exists supporting genetic testing for hereditary cardiomyopathy susceptibility is impactful in influencing treatment outcomes for symptomatic patients and those identified with anatomical abnormalities on imaging studies suggestive of hereditary cardiomyopathy. Adjunctive benefits include risk assessment of asymptomatic family members, differentiation of hereditary cardiomyopathy and/or arrhythmia from acquired (non-genetic) cardiomyopathy and/or arrhythmia, and recurrence risk calculation. Notable among sources of this evidence are:

- Among pathogenic variants covering 91 genes in 100 samples implicated in Mendelian diseases, 98.6% (91,743,296/93,062,298) of pathogenic variants demonstrated adequate depth for detection in exome sequencing, comparable to panel-based sequencing (LaDuca, 2017).
- A systematic review of 8,097 patients explored the relationship between genotypes and clinical phenotypes in dilated cardiomyopathy. Among other findings, average frequency of mutations was between 1% and 5%, and the mean age of dilated cardiomyopathy onset was the beginning of the fifth decade for all genes (Kayvanpour, 2017).
- In an analysis of family members from persons with hereditary cardiomyopathy, the 203 with a positive genetic test or family history reported a hereditary cardiomyopathy diagnosis in 17% (34 of 203) first-degree relatives who were screened. For the other 64 subjects, only 3% (2 of 64) of first-degree relatives had a hereditary cardiomyopathy diagnosis; 22 of 34 (65%) experienced adverse events related to cardiomyopathy ($P < .001$) (Ko, 2018).
- In a study of 289 young persons who died of sudden arrhythmia death syndrome over five years, genetic analysis showed 29% with positive heterozygous genetic variants (Mak, 2019).
- In a study of 152 children with cardiomyopathy, 81 underwent genetic testing. Of these, 48% had a positive result, and a molecular cause was identified in another 21%. A positive family history and hypertrophic cardiomyopathy subtype were associated with increased likelihood of genetic testing (Ware, 2021).
- A review of 398 pediatric patients with cardiomyopathy included 146 who underwent genetic testing, of whom 91 (62%) were gene-positive (Alashi, 2021).

- A review of 1,376 patients with hypertrophic cardiomyopathy found that 373 (27.1%) have a genetic variant, a proportion smaller than what had been previously reported. The likelihood of identifying a variant is significantly greater for young age, higher maximum wall thickness, positive family history, absence of hypertension, and presence of an implantable cardioverter-defibrillator (Hathaway, 2021).

A study of 6,179 participants with clinically genotyped hereditary cardiomyopathy showed that genetic variation in the majority of non-sarcomeric genes is not associated with the condition, as well as the etiology of the disorder being unknown in most patients. (Walsh, 2017).

A study comparing genetic testing in asymptomatic relatives of patients with dilated cardiomyopathy compared with periodical clinical surveillance concluded there is a 90% chance that testing is cost-effective (Catchpool, 2019).

A review of four studies (n = 327) of non-compaction cardiomyopathy participants (about 85% of which were adults) found 32% to be genetic with a mutation, and another 16% to be "probably genetic" without a mutation. Authors found MYH7, MYBPC3, and TTN mutations in 71% of cases. Mutations were more frequent in children (P = .04) and were associated with major adverse cardiac events (P = .025). Patients with MYH7 mutations were at low risk for major adverse cardiac events (P = .03). The article notes that identifying genetic and non-genetic cases can help predict outcomes and tailor care (van Waning, 2018).

A systematic review of 172 studies (n = 561) of geno- and phenotypes of non-compaction cardiomyopathy patients showed increased risk in children, compared to adults, for congenital heart defects and major adverse cardiac events (P < .001). Main causes in adults were single missense mutations in sarcomere genes; *MYH7* was involved in 48% of these cases. Children more frequently had an X-linked or mitochondrial inherited defect, typically multi-systemic disorders with severe outcome, suggesting the clinical approaches should be adjusted to age at presentation (van Waning, 2019).

In a systematic review of 29 studies (n = 9,486) of hypertrophic cardiomyopathy, which is the most common inherited cardiac condition younger than age 35, the main predictors of informative genetic testing were younger age, higher septal thickness, reverse septal curvature, family history of hypertrophic cardiomyopathy and sudden cardiac death, and the absence of hypertension. Authors note these predictors can help to decide which patients would benefit from a genetic test (Aziz, 2021).

In 2023, we identified no newly published, relevant literature to add to the policy. No policy changes are warranted.

References

On June 20, 2023, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were ("cardiomyopathy, dilated/genetics" (MeSH), "cardiomyopathy, hypertrophic, familial/genetics" (MeSH), "arrhythmogenic right ventricular dysplasia/genetics" (MeSH), and "hereditary cardiomyopathy." We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

8/2016: initial review date and clinical policy effective date: 10/2016

8/2017: Policy references updated.

8/2018: Policy references updated.

9/2019: Policy references updated. Policy ID changed to CCP.1252.

9/2020: Policy references updated.

9/2021: Policy references updated.

9/2022: Policy references updated.

9/2023: Policy references updated.