Genetic testing for hereditary cardiomyopathy

Clinical Policy ID: CCP.1252

Recent review date: 9/2024

Next review date: 1/2026

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

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Coverage policy

Genetic testing for hereditary cardiomyopathy susceptibility is clinically proven and, therefore, may be medically necessary for any of the following indications (Hershberger, 2018; Ommen, 2024; Towbin, 2019):

- 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 a 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 sequela 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 arrhythmogenic right ventricular cardiomyopathy. 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% to 30% of individuals. In most cases it is thought to be 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 is characterized by left ventricular enlargement and systolic dysfunction (ejection fraction < 50%). Three categories of dilated cardiomyopathy are acquired, syndromic, and non-syndromic (i.e., with no other system involvement). Manifestations may present at any age but usually in adults 40 to 60 years of age, and usually occur late in the disease course along with heart failure, arrhythmias, conduction system dysfunction, thromboembolic disease, or pregnancy. More than 30 gene variants have been identified in up to 30% to 35% of individuals with dilated cardiomyopathy classified as pathogenic, likely pathogenic, or of unknown significance (Hershberger, 2022).

Arrhythmogenic right ventricular cardiomyopathy is a progressive familial disease characterized pathologically as a progressive fibro-fatty replacement of the right ventricular musculature. Left ventricular involvement may occur in a minority of cases. The prevalence of clinical disease is estimated at 1:1,000-1,250 in the general population, largely derived from cohorts of European ancestry. A pathogenic variant is present in up to 66% of those with a clinical diagnosis of arrhythmogenic right ventricular cardiomyopathy, and in 2%-4% of cases, more than one pathogenic variant is present. Prognosis is worse in individuals with a prior history of sustained ventricular tachycardia or fibrillation and in in the presence of more than one pathogenic variant. Presence of this condition predisposes to ventricular tachycardia and sudden death in young individuals and athletes (McNally, 2023).

While genetic testing by Sanger sequencing for individual genes may be performed, multi-gene panels (gene-targeted panels) and comprehensive genomic testing through exome sequencing and genome sequencing may be used depending on the phenotype. 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

Guidelines

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 in the affected individual 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. Genetic testing is recommended to facilitate patient management and family screening. Multigene panel genetic testing is recommended over a serial single-gene testing because of the genetically heterogeneous nature of cardiomyopathy 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. Other notable recommendations include first-line genetic testing for genes with strong evidence for being disease-causing: MYH7, MYBPC3, TNNI3, TNNT2, TPM1, MYL2, MYL3, and ACTC1. Expanding to larger panels usually does not add diagnostic value. Genetic testing can be performed using various platforms, including gene panels, exome sequencing, or genome sequencing. If targeted gene panel testing does not reveal a causal variant, exome sequencing may provide a second-tier test, recognizing the possibility of incidental findings. A clinically actionable result (i.e., likely pathogenic or pathogenic) from genetic testing can clarify a diagnosis in the individual and offers the potential for cascade (predictive) testing of at-risk family members (Ommen, 2024).

The Heart Rhythm Society provided evidence-based, expert consensus statements on the management of arrhythmogenic cardiomyopathy. The Society affirmed the clinical utility of genetic testing to confirm a clinical diagnosis, provide disease–gene-specific risk stratification, tailor therapies, and enable variant-specific cascade genetic testing of appropriate relatives. The Society recommends genetic testing using comprehensive analysis of all established arrhythmogenic cardiomyopathy susceptibility genes with full coverage, for individuals and decedents with either a clinical or necropsy diagnosis of arrhythmogenic cardiomyopathy (Towbin, 2019).

Evidence review

Conclusive medical evidence exists supporting the utility of genetic testing for hereditary cardiomyopathy susceptibility 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.

Recent trends to increase gene panel sizes require careful appraisal of a gene-disease association to establish clinical utility. Appropriate classification of genes and their variants is essential to accurate genetic diagnosis. The National Institute of Health Clinical Genome Resource (ClinGen) established an evidence-based framework for identifying gene variants supporting the clinical validity of a gene-disease relationship (ClinGen, 2015).

Using this framework, ClinGen gene curation expert panels identified gene variants classified as having a definitive, strong, moderate, or limited, disputed, or refuted causal role in disease for hypertrophic cardiomyopathy, dilated cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy. Using this

framework, three evidence reviews, presented below, found that many genes commonly included in diagnostic test panels lack sufficient support for a causal association, may increase the likelihood of misclassification or inconclusive results being provided to practitioners, and may affect patient care.

Hypertrophic cardiomyopathy

Ingles (2019) examined 20 hypertrophic cardiomyopathy panels and four cardiomyopathy panels. The final curated list included 33 genes for hypertrophic cardiomyopathy and 24 genes for syndromes or conditions including left ventricular hypertrophy. Of the 33 genes classified for hypertrophic cardiomyopathy, eight (24.2%) were classified as definitive, three (9.1%) as moderate, 16 (48.5%) as limited, and six (18.2%) as no evidence. Genes classified as definitive were MYBPC3, MYH7, TNNT2, TNNI3, TPM1, ACTC1, MYL3, and MYL2.

Isolated left ventricular hypertrophy may be confused with a diagnosis of hypertrophic cardiomyopathy. Twelve of 24 syndromic genes were definitively associated with isolated left ventricular hypertrophy, one with a strong association, and one with a moderate association. The authors suggested inclusion of genes with moderate level and above for syndromes leading to isolated left ventricular hypertrophy.

Two-thirds of the curated genes had limited or no evidence of disease association and were represented inconsistently among currently offered diagnostic gene panels. Data from a large publicly accessible database showed nearly 30% of assertions made for hypertrophic cardiomyopathy in the final curated gene list were variants of unknown significance in genes with limited or no evidence of disease association (Ingles, 2019).

Dilated cardiomyopathy

Jordan (2021) curated 51 genes and 16 clinical genetic testing panels. Nineteen genes had substantial supportive evidence classified as definitive (11 genes), strong (one), or moderate (seven). Twelve genes from eight gene ontologies were classified as having definitive (BAG3, DES, FLNC, LMNA, MYH7, PLN, RBM20, SCN5A, TNNC1, TNNT2, TTN) or strong (DSP) evidence. Seven genes (ACTC1, ACTN2, JPH2, NEXN, TNNI3, TPM1, VCL) were classified as having moderate supportive evidence. Of these 19 genes, six were similarly classified for hypertrophic cardiomyopathy and three for arrhythmogenic right ventricular cardiomyopathy.

Most definitive genes were included in available genetic testing panels, along with many genes with limited or no human evidence. Eight gene panels (50%) offered testing for at least 75% of the genes curated for dilated cardiomyopathy. Results of this study describe the diverse genetic architecture of monogenic, primarily adult-onset, non-syndromic dilated cardiomyopathy, which can be used for diagnostic and predictive purposes. However, these 19 genes explain only 20% to 35% of cases.

Arrhythmogenic right ventricular cardiomyopathy

James (2021) identified 26 reported arrhythmogenic right ventricular cardiomyopathy genes, of which only six (PKP2, DSP, DSG2, DSC2, JUP, and TMEM43) had strong evidence and were classified as definitive for disease causation. There was moderate evidence for two genes (DES and PLN). The remaining 18 genes had limited or no evidence. Pathogenic or likely pathogenic variants in these eight genes should yield a major criterion for diagnosis. RYR2 was refuted as an arrhythmogenic right ventricular cardiomyopathy gene since clinical data and model systems exhibited a catecholaminergic polymorphic ventricular tachycardia phenotype.

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

In 2024, we added one expert consensus statement from the Heart Rhythm Society (Towbin, 2019), an updated guideline (Ommen, 2024), and three studies from ClinGen gene curation expert panels that identified gene and gene variants with sufficient evidence to establish a causal relationship in hereditary cardiomyopathies. No policy changes are warranted.

References

On July 19, 2024, 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.

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