Genetic Testing for Cardiac Disease

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➲ Instructions for Use

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Related Commercial/Individual Exchange Policies

- Cardiovascular Disease Risk Tests
- Chromosome Microarray Testing (Non-Oncology Conditions)
- Genetic Testing for Neurological Disorders

Community Plan Policy

- Genetic Testing for Cardiac Disease

Medicare Advantage Policy

- Molecular Pathology/Molecular Diagnostics/ Genetic Testing

Application

UnitedHealthcare Commercial

This Medical Policy applies to UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Policy applies to Individual Exchange benefit plans.

Coverage Rationale

Note: For chromosome microarray testing related to isolated, severe congenital heart disease, refer to the Medical Policy titled Chromosome Microarray Testing (Non-Oncology Conditions). For cardiomyopathies that present primarily as neuromuscular disorders, refer to the Medical Policy titled Genetic Testing for Neurological Disorders.

Pretest genetic counseling is recommended to inform persons being tested about the advantages and limitations of the test as applied to their unique situation.

Arrhythmias

Targeted Panel testing of five or more genes for the diagnosis of a heritable arrhythmia syndrome is proven and medically necessary in an individual with a confirmed or suspected diagnosis of any of the following conditions:

- Brugada syndrome
- Catecholaminergic polymorphic ventricular tachycardia
- Long QT syndrome (LQTS) when acquired causes have been ruled out and any of the following criteria are met:
  - Prolonged corrected QT interval (≥ 460 ms) on exercise or ambulatory electrocardiogram (Holter monitoring) or during pharmacological provocation testing; or
  - T-wave abnormalities on electrocardiogram that are suggestive of LQTS (e.g., torsades de pointes, T-wave alternans, notched T wave in three leads); or
  - Profound congenital, bilateral sensorineural hearing loss and prolonged corrected QT interval; or
  - Schwartz Score of ≥ 1.5 points
- Short QT syndrome

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Cardiomyopathies

Targeted Panel testing of five or more genes for the diagnosis of a heritable cardiomyopathy is proven and medically necessary in an individual with a confirmed or suspected diagnosis of any of the following conditions:

- Arrhythmogenic right ventricular dysplasia/cardiomyopathy
- Dilated cardiomyopathy, without an identifiable cause, when either of the following criteria are met:
  - Individual has cardiac conduction disease, such as atrioventricular block; or
  - Sudden cardiac death in a First-Degree Relative or Second-Degree Relative at age 45 years or younger
- Hypertrophic cardiomyopathy without an identifiable cause (e.g., valvular disease, hypertension, infiltrative or neuromuscular disorder)
- Left ventricular noncompaction cardiomyopathy

Thoracic Aortic Disease

Targeted Panel testing of five or more genes is proven and medically necessary for either of the following:

- Individual has confirmed thoracic aortic disease; or
- Thoracic aortic disease is suspected based on family history of thoracic aortic disease in a First-Degree Relative or Second-Degree Relative

Testing Based Only on Family History

Targeted Panel testing of five or more genes for the diagnosis of a heritable arrhythmia syndrome or cardiomyopathy is proven and medically necessary for either of the following:

- An asymptomatic individual who has a First-Degree Relative or Second-Degree Relative with any of the following conditions:
  - Arrhythmogenic right ventricular dysplasia/cardiomyopathy
  - Brugada syndrome
  - Catecholaminergic polymorphic ventricular tachycardia
  - Familial dilated cardiomyopathy
  - Hypertrophic cardiomyopathy
  - Left ventricular noncompaction cardiomyopathy
  - LQTS
  - Short QT syndrome
- An asymptomatic individual with a First-Degree Relative who experienced sudden cardiac death or near sudden death at age 45 years or younger

Comprehensive Panel tests that are intended to evaluate multiple genes associated with multiple categories of clinically distinct cardiomyopathies, arrhythmias, and/or aortic vascular disorders are unproven and not medically necessary due to insufficient evidence of efficacy.

All other genetic testing for cardiomyopathies, arrhythmias, or aortic vascular disease is unproven and not medically necessary due to insufficient evidence of efficacy.

Coronary Artery Disease

Genetic testing for coronary artery disease risk is unproven and not medically necessary due to insufficient evidence of efficacy, including but not limited to the following:

- Gene expression tests
- Microarray, polygenic risk scores, or other genetic profiles, such as:
  - Allelica PRS
  - CARDIO inCode-Score
  - Epi+Gen CHD
  - PrecisionCHD

Medical Records Documentation Used for Reviews

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. Medical records documentation may be required to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the service requested; refer to the guidelines titled Medical Records Documentation Used for Reviews.

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Definitions

Comprehensive Panel: An assay that simultaneously tests more than one gene associated with a variety of conditions, symptoms, or nonoverlapping clinical presentations (Rehder et al., 2021).

First-Degree Relative: First-Degree Relatives include parents, siblings, and offspring [National Comprehensive Cancer Network® (NCCN®), 2025].

Schwartz Score: A set of diagnostic criteria for long QT syndrome. The criteria are divided into three main categories, with a maximum score of 9 (Schwartz and Crotti, 2011).

Schwartz Score Calculation		
ECG[1]		**Points**
QTc[2]	≥ 480 ms	3
	460 to 479 ms	2
	450 to 459 ms (in male individuals)	1
QTc fourth minute of recovery from exercise stress test ≥ 480 ms		1
Torsades de pointes[3]		2
T-wave alternans		1
Notched T wave in three leads		1
Low heart rate for age[4]		0.5
Clinical History		**Points**
Syncope[3]	With stress	2
	Without stress	1
Congenital deafness		0.5
Family History		**Points**
Family members with definite LQTS[5]		1.0
Unexplained sudden cardiac death < 30 years in immediate family[5]		0.5
Total Score		

Scoring: ≤ 1.0 point = low probability of LQTS; 1.5 to 3.0 points = intermediate probability of LQTS; ≥ 3.5 points = high probability of LQTS.

1. In the absence of medications or disorders known to affect these electrocardiographic features.
2. QTc calculated by Bazett formula where QTc = QT/√RR.
3. Mutually exclusive.
4. Resting heart rate < 2nd percentile for age.
5. The same family member cannot be counted for both criteria.

Second-Degree Relative: Second-Degree Relatives include half-brothers/-sisters, aunts/uncles, grandparents, grandchildren, and nieces/nephews affected on the same side of the family (NCCN, 2025).

Targeted Panel: A curated assay that simultaneously tests more than one gene associated with a condition. A Targeted Panel may consist of multiple genes that are associated with one specific genetic condition or multiple genes that are associated with a symptom or nonspecific clinical presentation (Rehder et al., 2021).

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other policies and guidelines may apply.

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CPT Code	Description
0237U	Cardiac ion channelopathies (e.g., 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
0401U	Cardiology (coronary heart disease [CHD]), 9 genes (12 variants), targeted variant genotyping, blood, saliva, or buccal swab, algorithm reported as a genetic risk score for a coronary event
0439U	Cardiology (coronary heart disease [CHD]), DNA, analysis of 5 single-nucleotide polymorphisms (SNPs) (rs11716050 [LOC105376934], rs6560711 [WDR37], rs3735222 [SCIN/LOC107986769], rs6820447 [intergenic], and rs9638144 [ESYT2]) and 3 DNA methylation markers (cg00300879 [transcription start site {TSS200} of CNKSR1], cg09552548 [intergenic], and cg14789911 [body of SPATC1L]), qPCR and digital PCR, whole blood, algorithm reported as a 4-tiered risk score for a 3-year risk of symptomatic CHD
0440U	Cardiology (coronary heart disease [CHD]), DNA, analysis of 10 single-nucleotide polymorphisms (SNPs) (rs710987 [LINC010019], rs1333048 [CDKN2B-AS1], rs12129789 [KCND3], rs942317 [KTN1-AS1], rs1441433 [PPP3CA], rs2869675 [PREX1], rs4639796 [ZBTB41], rs4376434 [LINC00972], rs12714414 [TMEM18], and rs7585056 [TMEM18]) and 6 DNA methylation markers (cg03725309 [SARS1], cg12586707 [CXCL1, cg04988978 [MPO], cg17901584 [DHCR24-DT], cg21161138 [AHRR], and cg12655112 [EHD4]), qPCR and digital PCR, whole blood, algorithm reported as detected or not detected for CHD
0466U	Cardiology (coronary artery disease [CAD]), DNA, genome-wide association studies (564856 single-nucleotide polymorphisms [SNPs], targeted variant genotyping), patient lifestyle and clinical data, buccal swab, algorithm reported as polygenic risk to acquired heart disease
0617U	Cardiovascular (atherosclerotic cardiovascular disease [ASCVD]), DNA methylation analysis of more than 20,000 sites, whole blood, algorithm reported as positive or negative risk
81410	Aortic dysfunction or dilation (e.g., Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); genomic sequence analysis panel, must include sequencing of at least 9 genes, including FBN1, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, and MYLK
81411	Aortic dysfunction or dilation (e.g., Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); duplication/deletion analysis panel, must include analyses for TGFBR1, TGFBR2, MYH11, and COL3A1
81413	Cardiac ion channelopathies (e.g., 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 (e.g., 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 (e.g., hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy), genomic sequence analysis panel, must include sequencing of at least 5 cardiomyopathy-related genes (e.g., DSG2, MYBPC3, MYH7, PKP2, TTN)
81479	Unlisted molecular pathology procedure
81493	Coronary artery disease, mRNA, gene expression profiling by real-time RT-PCR of 23 genes, utilizing whole peripheral blood, algorithm reported as a risk score

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HCPCS Code	Description
S3865	Comprehensive gene sequence analysis for hypertrophic cardiomyopathy

Description of Services

Technologies used for genetic testing of cardiac and vascular syndromes and coronary artery disease can vary. Tests can include but are not limited to those that evaluate variations in genes, such as chromosome microarray analysis and next-

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generation sequencing, as well as others that assess gene products, such as gene expression assays and microRNA analysis. Results of genetic testing may assist individuals and health care providers with determination of a diagnosis or prognosis and identification of appropriate clinical interventions (Jabbari et al., 2013; Millat et al., 2014; Ladapo et al., 2017; Seidelmann et al., 2017). This policy addresses genetic test panels with five or more genes; other genetic testing for cardiovascular-related syndromes; and coronary artery disease genetic risk assessment and monitoring.

Clinical Evidence

The Weizman et al. (2024) retrospective observational study evaluated the diagnostic contribution of molecular genetic testing in patients with nonischemic sudden cardiac arrest and no overt left ventricular cardiomyopathy who were managed at two university hospitals between 2012 and 2021. The study population comprised 66 patients (mean age, 36.7 ±11.9 years; 54.5% men), all of whom survived to hospital admission and underwent standard clinical workup, including electrocardiography (ECG) and transthoracic echocardiography; 81.0% also underwent cardiac magnetic resonance (CMR) imaging. Patients were assigned to one of three subgroups based on phenotype: suspected channelopathy (n = 9); suspected arrhythmogenic cardiomyopathy (ACM; n = 20); or idiopathic ventricular fibrillation for those who did not present with phenotypic clues (n = 37). Genetic testing used a 72-gene sequencing panel that targeted channelopathy- and cardiomyopathy-associated genes, with variants classified according to American College of Medical Genetics and Genomics (ACMG) criteria. The median time from cardiac arrest to genetic testing was 6.0 months (IQR, 0.5-16.3 months). A genetic variant of interest was identified in 21 of the 66 patients (31.8%; 95% CI, 22.4%-45.3%). The test identified pathogenic or likely pathogenic variants in eight patients (12.1%) and variants of uncertain significance (VUSs) in 13 patients (19.7%). Among the 37 patients in the idiopathic ventricular fibrillation subgroup, pathogenic or likely pathogenic variants were found in five patients (13.5%), primarily in the *RYR2* (n = 3) and *SCN5A* (n = 2) genes; VUSs were found in nine patients (24.3%). None of the patients in the suspected channelopathy subgroup carried pathogenic or likely pathogenic variants, although two had VUSs in *RYR2* and *NKX2-5*. Among the 20 patients with suspected ACM, pathogenic or likely pathogenic variants were identified in three patients (15.0%; *PKP2*, *SCN5A*, and *DSC2*), and VUSs were found in two patients (10.0%; *TRPM4* and *DSG2*). No significant differences in age, sex, arrest rhythm, or resuscitation characteristics were observed between those with or without pathogenic or likely pathogenic variants. The authors concluded that genetic testing identified variants of interest in approximately one-third of patients with unexplained nonischemic sudden cardiac arrest, including a clinically relevant proportion without phenotypic clues, and may therefore contribute meaningfully to etiologic assessment and family screening. The findings are limited by the retrospective design, small sample size, incomplete clinical phenotyping at the time of testing, absence of segregation analyses for VUSs, and potential selection bias toward younger patients, which, together, limit generalizability and the strength of causal inferences.

Arrhythmias

Long QT Syndrome, Catecholaminergic Polymorphic Ventricular Tachycardia, and Short QT Syndrome

The Hermida et al. (2025) multicenter, observational cohort study evaluated the phenotypic spectrum that is associated with pathogenic or likely pathogenic *SCN5A* variants and quantified the prevalence of pleiotropy among variant carriers. From 2015 to 2023, 13,510 consecutive probands who were referred for inherited cardiac diseases across three tertiary centers underwent genetic testing using a custom panel. Of them, 9,960 probands had cardiomyopathies, and 3,550 had primary electrical disorders. Individuals carrying a single heterozygous pathogenic or likely pathogenic *SCN5A* variant were included, while those with additional pathogenic variants or missing clinical data were excluded. Phenotyping was based on clinical records at diagnosis and included ECG, sodium channel blocker challenge, echocardiography, CMR imaging, and electrophysiological studies, without standardized protocols. Across both probands and relatives (n = 495), 170 distinct pathogenic or likely pathogenic *SCN5A* variants were identified. Of these, 119 (70%) were associated exclusively with a single, well-established phenotype: Brugada syndrome, affecting 166 individuals; type 3 long QT syndrome (LQTS), affecting 31 individuals; progressive cardiac conduction disease, affecting 16 individuals; multifocal ectopic Purkinje-related premature contractions, affecting 19 individuals; and sick sinus syndrome, affecting seven individuals. Overlap syndromes or pleiotropy was associated with 32 genetic variants (19%), including nine variants causing mixed phenotypes in the same individual and 23 variants associated with intrafamilial or interfamilial pleiotropy. Brugada syndrome combined with progressive cardiac conduction disease or sick sinus syndrome was the most frequent overlap pattern. Atypical or unclear phenotypes were associated with 19 variants (11%), including eight variants identified in individuals with dilated cardiomyopathy (DCM); among these, DCM was secondary to ventricular hyperexcitability, atrial fibrillation, or myocarditis in several cases, and no cases of isolated primary DCM were identified. The authors concluded that most pathogenic or likely pathogenic *SCN5A* variants are associated with primary electrical disorders, predominantly Brugada syndrome, while approximately one-fifth have pleiotropy or overlap syndromes. This supports the need for comprehensive phenotypic evaluation of variant carriers. Functional data were available for 57 variants and demonstrated gain-of-function effects in type 3 LQTS and loss-of-function effects in Brugada syndrome, progressive cardiac conduction

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disease, sick sinus syndrome, and overlap phenotypes, with phenotype distribution influenced by variant location but not exclusively determined by it. The study is limited by its observational design, lack of standardized phenotyping, and absence of segregation data for atypical phenotypes, particularly DCM. The authors did not report a consolidated count that separated probands from relatives across the cohort or the reassignment of probands to cardiomyopathy or electrical disorder strata after variant adjudication and phenotypic review. This is notable because several individuals who were initially referred for cardiomyopathy were ultimately classified as having secondary or arrhythmia-associated DCM rather than a primary cardiomyopathic phenotype. These factors constrain inference regarding causality and penetrance and limit conclusions regarding rare cardiomyopathic presentations.

The Conte et al. (2024) international, retrospective, multicenter registry study evaluated atrial arrhythmias in patients with inherited arrhythmia syndromes, focusing on clinical presentation, genetic testing, heritability markers, and long-term outcomes. Consecutive patients with a guideline-defined inherited arrhythmia syndrome and electrocardiographically documented atrial arrhythmia were enrolled from 28 centers; those with a follow-up shorter than 12 months were excluded. The cohort comprised 522 patients, with a mean age of 56.8 ±19.8 years; 67.4% were male, and patients were followed up for a median of 8.3 years (IQR, 4.6-12.3 years). Overall, 355 patients (68.0%) had Brugada syndrome, 93 (18.0%) had LQTS, 42 (8.0%) had progressive cardiac conduction disease, and 14 (2.7%) had idiopathic ventricular fibrillation; 18 patients (3.4%) had short QT syndrome (SQTS), early repolarization syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT) together. Atrial fibrillation was present in 82.0% overall, most commonly paroxysmal atrial fibrillation (72.1%), while atrial flutter and atrial tachycardia each occurred in 9.0%. Atrial arrhythmia was the first documented clinical manifestation of the inherited arrhythmia syndrome in 52.0% of patients, and more than one atrial arrhythmia type was documented in 22.8% of those with available data. A family history of sudden cardiac death was reported in 27.2%, and a family history of atrial arrhythmias was reported in 17.4%. Genetic testing was performed in 336 patients (66.8%), identifying pathogenic or likely pathogenic variants in 73 (21.7%), with yields of 45.2% in LQTS, 55.5% in CPVT, 33.3% in progressive cardiac conduction disease, and 9.6% in Brugada syndrome; no variants were identified in SQTS, early repolarization syndrome, or idiopathic ventricular fibrillation, and no overlapping syndromes were reported. The primary end point, which was a composite of sudden cardiac death, sustained ventricular arrhythmia, or appropriate implantable cardioverter-defibrillator therapy, occurred in 61 patients (11.7%), corresponding to an annual incidence rate of 1.4% (95% CI, 0.8%-1.2%), with a median time to event of 3.1 years (IQR, 0.3-6.9 years). Appropriate implantable cardioverter-defibrillator therapy occurred in 40 patients (7.7%), ventricular fibrillation in 13 (2.5%), ventricular tachycardia in seven (1.3%), and sudden death in 11 (2.1%), with ventricular event rates below 1% per year in Brugada syndrome and LQTS and higher rates in progressive cardiac conduction disease and idiopathic ventricular fibrillation. Patients with an onset of atrial arrhythmia before reaching 20 years of age experienced ventricular events more frequently than those with later onset (21.1% vs 11.4%; odds ratio, 2.2; p = 0.043). The secondary end points included stroke or transient ischemic attack in 23 patients (4.4%), inappropriate implantable cardioverter-defibrillator therapy due to atrial arrhythmias in 15 (2.8%), and sinus node dysfunction in 60 (11.0%), with stroke incidence rates of 14.3% in progressive cardiac conduction disease and 11.1% in CPVT. The authors concluded that atrial arrhythmias often precede recognition of inherited arrhythmia syndromes and that earlier atrial arrhythmia onset may identify individuals at higher ventricular risk; however, the findings are limited by the retrospective design; absence of a comparison group without atrial arrhythmias; heterogeneous genetic testing and follow-up strategies; small numbers in rarer syndromes; and inability to assess genotype-phenotype differences between patients with inherited arrhythmia syndrome, with and without atrial arrhythmias, all of which indicate that well-designed, comparative studies are needed.

The Morgat et al. (2024) retrospective, observational cohort study evaluated whether genetic characterization of pathogenic *KCNQ1* variants improves risk stratification in patients with type 1 LQTS and Jervell and Lange-Nielsen syndrome (JLNS). Consecutive patients with class IV or V *KCNQ1* variants were referred to a single inherited arrhythmia center between September 1993 and January 2023 and were included, with an additional literature review to reclassify variants associated with JLNS. Medical history, ECG data, genotype, and lifelong follow-up for arrhythmic outcomes were collected through routine clinical care. Among 789 variant carriers, 30 had JLNS with homozygous or compound heterozygous variants, 161 were heterozygous carriers of JLNS-associated variants, and 550 were heterozygous carriers of non-JLNS *KCNQ1* variants. The mean age at diagnosis differed substantially across groups, with patients with JLNS diagnosed in early childhood (3.4 ±4.7 years) and heterozygous groups diagnosed in adulthood (26.7 ±21 and 26 ±21 years). The mean corrected QT interval (QTc) at diagnosis was longest in patients with JLNS (551 ±54 ms) compared with heterozygous JLNS (451 ±32 ms) and heterozygous non-JLNS carriers (467 ±36 ms). The median lifelong follow-up exceeded 3 decades. During follow-up, arrhythmic events occurred in 87% of patients with JLNS, 13% of heterozygous JLNS variant carriers, and 33% of heterozygous non-JLNS carriers, while severe arrhythmic events occurred in 30%, 0.6%, and 4%, respectively. Heterozygous carriers of JLNS variants had a significantly lower risk of arrhythmic events than heterozygous non-JLNS carriers [hazard ratio (HR), 0.34; 95% CI, 0.22-0.54; p < 0.01], which was a finding that persisted after multivariable adjustment (HR, 0.43; 95% CI, 0.27-0.69; p < 0.01). Among heterozygous patients, haploinsufficiency was associated with reduced risk (HR, 0.60; 95% CI, 0.37-0.97; p = 0.04); pore-localized variants were associated with increased risk (HR, 1.61; 95% CI, 1.14-2.26; p < 0.01); and C-terminal localization was associated with

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reduced risk (HR, 0.67; 95% CI, 0.46-0.98; p = 0.04). The authors concluded that heterozygous carriers of JLNS-associated *KCNQ1* variants represent a substantial proportion of individuals diagnosed with type 1 LQTS and have a lower risk of cardiac arrhythmic events than other individuals with type 1 LQTS. The findings are limited by the retrospective, single-center design; absence of randomization or masking; and limited power for rare subgroups, all of which constrain the strength and generalizability of the conclusions.

The Bjelic et al. (2024) study used a registry-based, observational cohort design to derive and test a sex-specific risk prediction model in male adolescents with genetically confirmed potassium channel–mediated LQTS. The investigators analyzed 611 male individuals who were aged 10 to 20 years with type 1 (*KCNQ1*) or type 2 (*KCNH2*) LQTS and enrolled in an international LQTS research registry; those with multiple genetic mutations or missing key data were excluded. Follow-up spanned a mean of 9.9 ±2.5 years, with surveillance from ages 10 to 20 years or until death if prior to age 20 years. The primary objective was to estimate the burden of recurrent cardiac events, which were defined as syncope, aborted cardiac arrest, or appropriate implantable cardioverter-defibrillator therapy; the secondary objective assessed the first occurrence of a life-threatening event, which was defined as aborted cardiac arrest, appropriate implantable cardioverter-defibrillator therapy, or LQTS-related sudden cardiac death. Genotype and mutation location, QTc dichotomized at 500 milliseconds, history of syncope before age 10 years, and time-dependent β-blocker therapy were incorporated in the evaluation of total event burden. In all, 16 prespecified genotype-phenotype combinations were collapsed into three risk strata: low risk [n = 452 (74%)], intermediate risk [n = 86 (14%)], and high risk [n = 73 (12%)]. During follow-up, 270 recurrent cardiac events occurred; 12% of individuals experienced one event, and 9.3% experienced two or more events. Compared with the low-risk group, intermediate-risk individuals had a higher rate of recurrent cardiac events (HR, 2.06; 95% CI, 1.27-3.36), and high-risk individuals had a substantially higher rate (HR, 5.17; 95% CI, 3.06-8.72). At age 20 years, the mean cumulative number of cardiac events per person was 0.3 in the low-risk group, 0.6 in the intermediate-risk group, and 1.4 in the high-risk group. When the model was applied to the first life-threatening event, the risk remained higher in the intermediate-risk group (HR, 3.03; 95% CI, 1.04-8.86) and the high-risk group (HR, 4.05; 95% CI, 1.36-12.05) compared with the low-risk group, with corresponding 10-year adjusted probabilities of 2%, 6%, and 8%. No significant interactions were observed between β-blocker therapy and risk strata for either end point. The authors concluded that a personalized genotype-phenotype risk model can stratify male adolescents with type 1 or type 2 LQTS into clinically distinct risk groups for recurrent cardiac events and life-threatening outcomes; additionally, it may support sex-specific management strategies. The findings are limited by the nonrandomized, registry-based design; lack of external validation; reliance on historical treatment patterns with heterogeneous β-blocker use; and relatively small number of life-threatening events, all of which constrain precision and generalizability.

In a Clinical Utility Evaluation, Hayes indicated that evidence that demonstrates improved health outcomes in individuals who had undergone genetic testing after clinical diagnosis of CPVT was insufficient and recommended additional investigation (Hayes, 2018a; updated 2022). For family members of individuals with CPVT, Hayes found probable clinical utility, stating that genetic testing for CPVT can lead to preventative treatment and activity restrictions when family members test positive. The Hayes report also stated that genetic testing is most helpful when the familial variant is identified in a clinically diagnosed individual (Hayes, 2018b; updated 2022).

Brugada Syndrome

The Tuijnenburg et al. (2025) retrospective, multicenter, observational cohort study evaluated the long-term arrhythmic risk and predictors of arrhythmic events in patients carrying a pathogenic or likely pathogenic loss-of-function variant in *SCN5A*. Consecutive probands and family members identified through genetic testing at two tertiary referral centers between 1996 and 2022 were included, which yielded a cohort of 615 patients (mean age, 36 ±18.5 years; 56.7% male); of these patients, 242 were probands and 504 (82.0%) were asymptomatic at the time of genetic diagnosis. Baseline classification as symptomatic required a history of aborted cardiac arrest, sustained ventricular tachycardia, symptomatic or documented atrial tachyarrhythmia or bradyarrhythmia, or arrhythmogenic syncope. Baseline data included clinical characteristics and ECG parameters, with longitudinal follow-up through periodic outpatient evaluations every 1 to 3 years. Arrhythmic events during follow-up were prespecified as sudden unexplained death, aborted cardiac arrest, documented ventricular fibrillation, sustained ventricular tachycardia, or appropriate implantable cardioverter-defibrillator therapy. Over a median follow-up of 9.5 years (IQR, 5.0-14.3 years), 41 patients (6.7%) experienced an arrhythmic event, corresponding to an overall annual event rate of 0.7%. Event rates differed markedly by baseline symptom status, with 26 of 111 symptomatic patients (23.4%; 2.0% per year) and 15 of 504 asymptomatic patients (3.0%; 0.3% per year) experiencing events (rate ratio, 6.1; 95% CI, 3.2-11.7; p < 0.001). In multivariable Cox regression across the full cohort, baseline symptoms (HR, 6.78; 95% CI, 3.30-13.95; p < 0.001), male sex (HR, 2.84; 95% CI, 1.14-7.03; p = 0.024), and longer baseline QRS duration (HR, 1.03 per ms; 95% CI, 1.01-1.05; p < 0.001) were independent predictors of arrhythmic events, whereas a spontaneous type 1 Brugada ECG pattern and proband status were not independent predictors after adjustment. Among asymptomatic patients, male sex (HR, 5.44; 95% CI, 1.17-25.38; p = 0.031) and longer QRS duration (HR, 1.03 per ms; 95% CI, 1.01-1.05; p = 0.005) emerged as predictors, and no arrhythmic events occurred in asymptomatic women with a QRS of < 100 ms during follow-up. Electrophysiology study inducibility of ventricular

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arrhythmias was not associated with future events (p = 0.610), and no differences in arrhythmic risk were observed by *SCN5A* variant type. The authors concluded that long-term arrhythmic risk in *SCN5A* loss-of-function carriers is strongly stratified by baseline symptoms, sex, and QRS duration, regardless of a Brugada syndrome diagnosis, and that asymptomatic women with normal QRS intervals represent a particularly low-risk subgroup. The findings of this study are limited by the retrospective design, potential selection and information biases, heterogeneity in follow-up duration and management, and absence of randomization or standardized intervention protocols, which constrain causal inference and generalizability.

The Doundoulakis et al. (2024) systematic review and meta-analysis of observational cohort and case-control studies through January 2024 evaluated the association between *SCN5A* rare variants and arrhythmic risk in individuals with Brugada syndrome. In all, 17 studies, involving 3,568 individuals with Brugada syndrome, were included; of these individuals, 3,030 underwent *SCN5A* genetic testing, with findings of a rare *SCN5A* variant in 750 individuals (24.7%). Most studies were observational; there was a mix of single-center and multicenter designs without randomization or masking, and the studies included predominantly adult, largely male populations from European and Asian cohorts, with a small number of pediatric studies. Brugada syndrome was diagnosed based on ECG according to contemporaneous guidelines. Major arrhythmic events were defined as ventricular tachycardia or fibrillation, appropriate implantable cardioverter-defibrillator therapy, aborted cardiac arrest, or sudden cardiac death. Subgroup analyses examined age, ethnicity, variant classification, and loss-of-function status. Across pooled analyses, individuals with *SCN5A* variants had a worse clinical phenotype than noncarriers, with higher proportions of spontaneous type 1 ECGs (45% vs 40%; odds ratio, 1.83; 95% CI, 1.32-2.53), syncope (39% vs 29%; odds ratio, 1.60; 95% CI, 1.16-2.21), aborted cardiac arrest (16% vs 10%; odds ratio, 2.04; 95% CI, 1.24-3.34), and documented ventricular tachyarrhythmias (27% vs 18%; odds ratio, 2.06; 95% CI, 1.29-3.28). ECG intervals were longer in *SCN5A* variant carriers, including PR interval (mean difference, 29.0 ms; 95% CI, 19.9-38.2 ms) and QRS duration (mean difference, 11.1 ms; 95% CI, 7.7-14.5 ms), while QTc duration did not differ significantly. In the 12 studies that reported the occurrence of major arrhythmic events, which comprised 1,914 individuals and had a pooled mean follow-up of 59.6 months, *SCN5A* variant status was associated with a higher risk of major arrhythmic events (pooled odds ratio, 2.14; 95% CI, 1.53-2.99; I^2 = 29%). Loss-of-function *SCN5A* variants conferred a higher risk of major arrhythmic events than both non–loss-of-function variants (odds ratio, 4.05; 95% CI, 1.54-10.64) and noncarriers (odds ratio, 3.40; 95% CI, 1.59-7.60), whereas non–loss-of-function variants were not associated with increased risk. The authors concluded that *SCN5A* loss-of-function variant carriers have more severe clinical and electrophysiological features and have higher arrhythmic risk. These findings are limited by the observational design of the included studies and heterogeneity in variant classification and diagnostic criteria over time. Well-designed, prospective comparative studies are needed.

The Pannone et al. (2024) prospective, single-center, observational cohort study evaluated the diagnostic yield and prognostic significance of genetic variants that were identified through a large next-generation sequencing panel in participants with Brugada syndrome who were enrolled in an academic medical center registry between 1992 and 2022. Inclusion required a Brugada syndrome diagnosis based on a spontaneous type I ECG or a positive ajmaline challenge; genetic testing, with a broad panel of arrhythmia and cardiomyopathy genes; and a finding associated with a recent variant reclassification under current ACMG guidelines. Records for a total of 500 participants were analyzed; the mean age at diagnosis was 38.9 ±16.9 years, and 49.0% of participants were male. Genetic sequencing had identified a pathogenic or likely pathogenic *SCN5A* variant in 104 participants (20.8%), of whom 69 carried missense variants, and 35 carried predicted loss-of-function variants. An additional 75 participants (15.0%) carried variants in non-*SCN5A* genes, with 17 classified as predicted loss of function and 58 as missense. No reportable variants were found in 321 participants (64.2%). Follow-up was conducted every 6 months to document clinic visits, device interrogations, or Holter monitoring, with a median total follow-up period of 84.0 months (IQR, 45.7-138.0 months). The primary end point was ventricular arrhythmia occurrence, defined as sudden cardiac death, aborted sudden cardiac death, sustained ventricular tachycardia, ventricular fibrillation, or appropriate implantable cardioverter-defibrillator therapy; atrial fibrillation was a secondary outcome. Over the course of follow-up, 48 participants (9.6%) experienced a ventricular arrhythmia, with the first event occurring after a median of 53.5 months. Atrial fibrillation occurred in 83 participants (16.6%), and eight deaths were reported, including two sudden cardiac deaths. Kaplan-Meier analyses demonstrated higher ventricular arrhythmia–free survival in participants without reportable variants compared with those carrying pathogenic or likely pathogenic *SCN5A* variants (92.7% vs 81.7%; log-rank p = 0.031). When stratified by variant type, participants with predicted loss-of-function variants in *SCN5A* had significantly lower ventricular arrhythmia–free survival than both *SCN5A* missense variant carriers (68.6% vs 88.4%; pairwise log-rank p = 0.045) and those without variants (68.6% vs 92.7%; p = 0.001), whereas missense variant carriers did not differ from variant-negative participants (p = 0.64). Similar results were observed when predicted loss-of-function variants in non-*SCN5A* genes were included; participants with any predicted loss-of-function variant in *SCN5A* or non-*SCN5A* genes had lower ventricular arrhythmia–free survival than missense variant carriers or participants with no variants (71.2% vs 91.3% and 93.1%, respectively), with no difference between missense variant carriers and variant-negative participants (p = 0.91). In a multivariable Cox regression, independent predictors of ventricular arrhythmia included a history of syncope (HR, 2.51; 95% CI, 1.41-4.48), prior aborted sudden cardiac death

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(HR, 12.47; 95% CI, 6.88-22.61), inducibility of ventricular arrhythmias at electrophysiological study (HR, 4.24; 95% CI, 2.25-8.00), and carriage of a predicted loss-of-function variant in *SCN5A* or non-*SCN5A* genes (HR, 2.61; 95% CI, 1.39-4.9). The authors concluded that genetic testing using a large gene panel and standardized variant classification yields pathogenic or likely pathogenic *SCN5A* variants in approximately one-fifth of individuals with Brugada syndrome and that predicted loss-of-function variants, regardless of gene, are associated with a worse ventricular arrhythmic prognosis and independently predict arrhythmic events. The findings are limited by the study's single-center, observational design; possible referral bias; relatively small numbers of predicted loss-of-function variant carriers; and lack of routine functional validation of variants, all of which limit causal inference and generalizability.

The Kukavica et al. (2024) longitudinal cohort study evaluated nonmodifiable risk factors for life-threatening arrhythmic events in Brugada syndrome by analyzing 2,182 consecutive, unrelated individuals who were diagnosed between 1994 and 2023 and enrolled in a single national registry. Diagnosis was based on a type 1 ECG pattern, and clinical data were prospectively collected. All individuals underwent genetic screening for pathogenic or likely pathogenic *SCN5A* variants; genotyping of three single-nucleotide variants was used to construct a weighted polygenic risk score (PRS) for Brugada syndrome. The primary end point was a composite of sudden cardiac death, aborted cardiac arrest, or hemodynamically nontolerated ventricular tachycardia, which was assessed from birth through diagnosis and follow-up. At diagnosis, 4% of the study population had previously experienced a life-threatening arrhythmic event, and 16% had unexplained syncope; 51% had a spontaneous type 1 pattern. From birth to the last follow-up, 123 of 2,182 individuals (6%) experienced a first life-threatening arrhythmic event at a median age of 43.2 years; 64% of these occurred before diagnosis. Male sex was associated with higher risk (HR, 3.6; 95% CI, 1.9-6.9; p = 0.0001), as were missense *SCN5A* mutations localized to Brugada-enriched channel domains (HR, 2.3; 95% CI, 1.2-4.3; p = 0.008), nonmissense *SCN5A* mutations (HR, 3.2; 95% CI, 1.8-5.7; p < 0.001), and higher PRS for Brugada syndrome (HR, 1.3; 95% CI, 1.0-1.6; p = 0.041). Missense variants that were outside enriched domains were not associated with increased risk (HR, 0.4; 95% CI, 0.1-2.7; p = 0.323). Family history of sudden death was not associated with a first life-threatening arrhythmic event (HR, 1.1; 95% CI, 0.7-1.8; p = 0.597). Using the coefficients from this model, the authors derived a composite nonmodifiable risk score that ranged from 0.00 to 3.09, which showed a strong association with lifetime risk of life-threatening arrhythmic event (HR, 2.7; 95% CI, 2.0-3.7; p < 0.0001), with tertile stratification identifying distinct risk profiles. In a prospective follow-up analysis in 1,928 individuals who were observed for a mean of 5.7 ±4.7 years after diagnosis, 65 individuals experienced a life-threatening arrhythmic event. Nonmodifiable risk remained independently associated with follow-up events (HR, 1.8; 95% CI, 1.1-2.7; p = 0.014) after adjustment for established clinical predictors, including prior life-threatening arrhythmic events (HR, 13.8; 95% CI, 8.1-23.7; p < 0.0001), unexplained syncope (HR, 4.1; 95% CI, 2.4-6.8; p < 0.0001), and spontaneous type 1 pattern at diagnosis (HR, 2.1; 95% CI, 1.2-3.8; p = 0.010). The authors concluded that male sex, *SCN5A* mutation type and location, and PRS together define an individual's nonmodifiable risk, which is independently associated with life-threatening arrhythmic outcomes regardless of symptoms or ECG pattern. The findings are limited by the observational design, lack of randomization or masking, and potential unmeasured confounding. External validation is needed.

A Hayes Clinical Utility Evaluation suggests that insufficient evidence exists to support the use of genetic testing in individuals who have been clinically diagnosed with Brugada syndrome, as no existing studies were found that would indicate improved health outcomes in the affected individual that were related to such testing (Hayes, 2018c; updated 2022). Limited evidence supports the use of genetic testing in family members of individuals with Brugada syndrome (Hayes, 2018d; updated 2022).

Atrial Fibrillation

There is currently insufficient evidence to support the use of genetic testing in the diagnosis or management of atrial fibrillation. Additional studies are needed to demonstrate clinical utility.

The Laws et al. (2026) observational single-center study evaluated the clinical and therapeutic impact of comprehensive genetic evaluation in individuals with early-onset atrial fibrillation who were managed in a dedicated atrial fibrillation precision medicine clinic. Individuals who were diagnosed with atrial fibrillation before age 60 years were referred based on clinical suspicion or automated electronic medical record alerts and underwent standardized phenotyping, including history, physical examination, 12-lead ECG, ambulatory monitoring, cardiac imaging, pedigree construction, and clinical genetic testing using cardiomyopathy and arrhythmia gene panels. Among 264 referred individuals, 242 completed genetic testing; the median age at evaluation was 47 years, and the median age at atrial fibrillation diagnosis was 39 years. The study population was 29% female, and 89% were of White European ancestry. Pathogenic or likely pathogenic variants were identified in 48 of the 242 tested individuals (20%). The most frequent variants involved DCM-associated genes, predominantly *TTN*, with smaller numbers involving ACM, hypertrophic cardiomyopathy (HCM), and channelopathy genes. Multivariable logistic regression, which was adjusted for age at atrial fibrillation diagnosis, sex, and time to testing, showed significant associations between positive genetic testing and a prior cardiomyopathy diagnosis (odds ratio, 5.3; 95% CI, 2.1-13.3; p < 0.001), infranodal conduction disease on ECG (odds ratio, 3.3; 95% CI, 1.3-8.2; p = 0.011), elevated myocardial T1 time on CMR imaging (odds ratio, 4.0; 95% CI, 1.5-11.2; p = 0.007), and late gadolinium

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enhancement (odds ratio, 2.4; 95% CI, 1.0-6.0; p = 0.050). Obstructive sleep apnea (odds ratio, 0.4; 95% CI, 0.2-0.8; p = 0.013) and a normal ECG (odds ratio, 0.5; 95% CI, 0.3-1.0; p = 0.042) were associated with a lower likelihood of a positive genetic test. Ventricular phenotypic expression was present in 29 of 52 genotype-positive individuals (56%), which varied by genetic subgroup, including 54% for DCM genes, 89% for ACM genes, 40% for HCM genes, and 50% for channelopathy genes. Genetic evaluation led to changes in clinical management in 27 of the 52 individuals with pathogenic or likely pathogenic variants (52%) compared with 11% among those with genotype-negative atrial fibrillation overlap syndromes. Management changes included initiation or optimization of guideline-directed medical therapy in 16 individuals, implantation of seven new implantable cardioverter-defibrillators, initiation of anticoagulation in the individuals who were newly diagnosed with HCM or ACM, medication avoidance or precautions in channelopathy-associated variants, and directed lifestyle or exercise recommendations. The authors concluded that genetic testing frequently altered downstream clinical management, particularly in genotype-positive individuals. The findings are limited by the single-center design; a predominantly White European population; limited power for subgroup analyses; absence of randomization or a control group; and lack of long-term outcome data, all of which underscore the need for larger, more diverse comparative studies that include extended follow-up.

Yoneda et al. (2021) conducted a prospective, observational cohort study to assess the yield of genetic testing in early-onset atrial fibrillation. The study included 1,293 participants who were diagnosed with atrial fibrillation before age 66 years and enrolled at a single academic medical center from November 1999 and June 2015. All participants underwent whole-genome sequencing, with analysis of 145 genes that are commonly included on commercial cardiomyopathy and arrhythmia panels. Variant interpretation was performed using automated pipelines, followed by manual review by independent, blinded reviewers. Variants were classified according to ACMG criteria, and disease-associated variants were defined as pathogenic or likely pathogenic variants in genes that are associated with autosomal dominant or X-linked dominant disorders. Genetic testing identified disease-associated variants in 10.1% of participants, while 62.8% had VUSs; 7.1% were heterozygous carriers of autosomal recessive disorders, and 20% had no reportable variants. The prevalence of disease-associated variants was highest among participants who were diagnosed before age 30 years and lowest among those who were diagnosed after age 60 years, with variants more frequently associated with inherited cardiomyopathy syndromes than inherited arrhythmias. The authors concluded that these findings support the use of genetic testing in early-onset atrial fibrillation. Limitations include variability in ACMG variant classification, limited evidence to support the clinical relevance of some genes included on commercial panels, and limited generalizability due to the single-center design and predominantly European ancestry in the cohort.

Clinical Practice Guidelines

American College of Cardiology (ACC)/American Heart Association (AHA)/American College of Clinical Pharmacy (ACCP)/Heart Rhythm Society (HRS)

The ACC/AHA/ACCP/HRS guidelines on the diagnosis and management of atrial fibrillation (Joglar et al., 2024) include the following:

- For patients who develop atrial fibrillation before the age of 45 years without clear risk factors, it may be reasonable to consider genetic counseling, genetic testing for rare pathogenic variants (most commonly *TTN, MYH7, MYH6, LMNA*, and *KCNQ1*), and monitoring for cardiomyopathy or arrhythmia syndromes [class of recommendation: 2b (weak); level of evidence: B-NR (nonrandomized)].
- PRSs can suggest a higher risk of atrial fibrillation, but the use of genetic testing to impact clinical surveillance, management, and outcomes remains uncertain.

American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS)

The ACC, AHA, and HRS published guidelines on the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death (Al-Khatib et al., 2018), which include the following statements and recommendations:

- The availability of genetic testing for inherited arrhythmia syndromes can provide an opportunity to confirm a suspected diagnosis for the proband and offer cascade screening of potentially affected family members when a disease-causing mutation is identified in the proband.
- Genotyping is frequently most useful when a pathogenic mutation is identified in the proband, such that screening can be applied to relatives who are in a preclinical phase, allowing institution of lifestyle changes, therapy, or ongoing monitoring in those who are gene mutation positive.
- In young patients (< 40 years of age) with unexplained cardiac arrest, unexplained near drowning, or recurrent exertional syncope who do not have ischemic or other structural heart disease, further evaluation for genetic arrhythmia syndromes is recommended [class of recommendation: I (strong); level of evidence: B-NR (nonrandomized)].

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- In patients with nonischemic cardiomyopathy who develop conduction disease or left ventricular dysfunction at less than 40 years of age or have a family history of nonischemic cardiomyopathy or sudden cardiac death in a first-degree relative (< 50 years of age), genetic counseling and genetic testing are reasonable to detect a heritable disease that may clarify prognosis and facilitate cascade screening of relatives [class of recommendation: IIa (moderate); level of evidence: C-EO (expert opinion)].
- In selected first-degree relatives of patients with arrhythmogenic right ventricular cardiomyopathy (ARVC), clinical screening for the disease is recommended, along with genetic counseling and genetic testing, if the proband has a disease-causing mutation [class of recommendation: I (strong); level of evidence: B-NR (nonrandomized)].
- In first-degree relatives of patients with HCM due to a known causative mutation, genetic counseling and mutation-specific genetic testing are recommended [class of recommendation: I (strong); level of evidence: B-NR (nonrandomized)].
- In patients with clinically suspected or diagnosed HCM, genetic counseling and genetic testing are reasonable [class of recommendation: IIa (moderate); level of evidence: B-NR (nonrandomized)].
- In first-degree relatives of patients who have a causative mutation for LQTS, CPVT, SQTS, or Brugada syndrome, genetic counseling and mutation-specific genetic testing are recommended [class of recommendation: I (strong); level of evidence: B-NR (nonrandomized)].
- In patients with clinically diagnosed LQTS, genetic counseling and genetic testing are recommended [class of recommendation I (strong); level of evidence: B-NR (nonrandomized)].
- In patients with CPVT and clinical ventricular tachycardia or exertional syncope, genetic counseling and genetic testing are reasonable [class of recommendation: IIa (moderate); level of evidence: B-NR (nonrandomized)].
- In patients with suspected or established Brugada syndrome, genetic counseling and genetic testing may be useful to facilitate cascade screening of relatives [class of recommendation: IIb (weak); level of evidence: C-EO (expert opinion)].
- In patients with an early repolarization pattern on ECG, genetic testing is not recommended [class of recommendation: III no benefit (moderate); level of evidence: B-NR (nonrandomized)].
- In patients with SQTS, genetic testing may be considered to facilitate screening of first-degree relatives [class of recommendation: IIb (weak); level of evidence: C-EO (expert opinion)].
- In first-degree relatives of patients who experienced sudden cardiac death and were 40 years of age or younger, cardiac evaluation is recommended, with genetic counseling and genetic testing performed as indicated by clinical findings [class of recommendation: I (strong); level of evidence: B-NR (nonrandomized)].

European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS)

In an expert consensus statement on genetic testing for cardiac disease, the EHRA, HRS, APHRS, and LAHRS (Wilde et al., 2022) provide the following recommendations for genetic testing in arrhythmias:

Long QT Syndrome

- Molecular genetic testing for definitive disease-associated genes (currently *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, and *KCNE2*) should be offered to all patients with acquired LQTS who experienced drug-induced torsades de pointes, are aged below 40 years, and have a QTc of > 440 ms (male) and > 450 ms (female) in the absence of a culprit drug. (Supported by strong observational evidence and authors' consensus.)
- Cascade family screening for the presence of pertinent variants should be considered when QT-prolonging drugs are or could be prescribed. (Some evidence and general agreement favor usefulness/efficacy of a test.)
- Molecular genetic testing for definitive disease-associated genes (currently *KCNQ1, KCNH2, SCN5A, CALM1, CALM2*, and *CALM3*) should be offered to all index patients with a high probability of diagnosis of LQTS, based on examination of the patient's clinical history, family history, and ECG characteristics that were obtained at baseline, during ECG Holter recording, and during an exercise stress test (Schwartz score ≥ 3.5). (Supported by strong observational evidence and authors' consensus.)
- Analysis of specific genes should be offered to patients with a specific diagnosis, as follows:
  - *KCNQ1* and *KCNE1* in patients with JLNS.
  - *CACNA1C* in Timothy syndrome.
  - *KCNJ2* in Andersen-Tawil syndrome.
  - *TRDN* in patients who are suspected to have triadin knockout syndrome. (Supported by strong observational evidence and authors' consensus.)
- An analysis of *CACNA1C* and *KCNE1* may be performed in all index patients in whom a cardiologist has established a diagnosis of LQTS with a high probability, based on examination of the patient's clinical history, family history, and ECG characteristics that were obtained at baseline, during ECG Holter recording, and during an exercise stress test (Schwartz score ≥ 3.5). (Some evidence and general agreement favor usefulness/efficacy of a test.)

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- Variant-specific genetic testing is recommended for family members and appropriate relatives following the identification of the disease-causing variant. (Supported by strong observational evidence and authors' consensus.)
- Predictive genetic testing in related children is recommended from birth onward (any age). (Supported by strong observational evidence and authors' consensus.)

Catecholaminergic Polymorphic Ventricular Tachycardia

- In any patient who satisfies the diagnostic criteria for CPVT (such as class 1 clinical diagnosis or CPVT diagnostic score > 3.5), molecular genetic testing is recommended for the currently established CPVT-susceptibility genes, with definite/strong evidence: *RYR2, CASQ2, CALM1-3, TRDN, and TECRL*. (Supported by strong observational evidence and authors' consensus.)
- In phenotype-positive patients with CPVT who are negative for those established CPVT-susceptibility genes, genetic testing may be considered for CPVT phenocopies that result from pathogenic variants in the *KCNJ2, SCN5A,* and *PKP2* genes. (Some evidence and general agreement favor usefulness/efficacy of a test.)
- In patients with a modest phenotype for CPVT (i.e., CPVT diagnostic score ≥ 2 but < 3.5), genetic testing may be considered for the established CPVT-susceptibility genes with definite/strong evidence: *RYR2, CASQ2, CALM1-3*, *TRDN*, and *TECRL*. (Some evidence and general agreement favor usefulness/efficacy of a test.)
- Variant-specific genetic testing is recommended for family members and appropriate relatives following the identification of the disease-causative variant. (Supported by strong observational evidence and authors' consensus.)
- Predictive genetic testing in related children who are at risk of inheriting a pathogenic/likely pathogenic variant is recommended from birth onward (any age). (Supported by strong observational evidence and authors' consensus.)

Brugada Syndrome

- Genetic testing with sequencing of *SCN5A* is recommended for an index case that is diagnosed with Brugada syndrome with a type I ECG in standard or high precordial leads that occurs either spontaneously or is induced by sodium-channel blockade in the presence of supporting clinical features or family history. (Supported by strong observational evidence and authors' consensus.)
- Rare variants in genes with disputed or refuted gene-disease clinical validity should not be reported routinely for Brugada syndrome genetic testing in a diagnostic setting. (There is evidence or general agreement not to recommend a test.)
- Targeted sequencing of VUSs in *SCN5A* with a population allele frequency of < 1×10^{-5} that are identified in an index case can be considered concurrently with phenotyping for family members, following genetic counseling, to assess variant pathogenicity through cosegregation analysis. (Some evidence and general agreement favor usefulness/efficacy of a test.)
- Variant-specific genetic testing is recommended for family members and appropriate relatives following the identification of the disease-causative variant. (Supported by strong observational evidence and authors' consensus.)
- Predictive genetic testing (of pathogenic *SCN5A* variants) in related children is recommended from birth onward (any age). (Some evidence and general agreement favor usefulness/efficacy of a test.)

Short QT Syndrome

- In any patient who satisfies the diagnostic criteria for SQTS (such as class 1 clinical diagnosis or SQTS diagnostic score > 4), molecular genetic testing is recommended for the definitive disease-associated genes (currently *KCNH2* and *KCNQ1*). (Supported by strong observational evidence and authors' consensus.)
- Testing of *KCNJ2* and *SLC4A3* may be performed in all index patients in whom a cardiologist has established, with a high probability, a diagnosis of SQTS, based on examination of the patient's clinical history, family history, and ECG characteristics that were obtained at baseline, during ECG Holter recording, and during an exercise stress test (SQTS diagnostic score ≥ 4). (Some evidence and general agreement favor usefulness/efficacy of a test.)
- Variant-specific genetic testing is recommended for family members and appropriate relatives following the identification of the disease-causative variant. (Supported by strong observational evidence and authors' consensus.)
- Predictive genetic testing in related children may be considered in specific settings. (Some evidence and general agreement favor usefulness/efficacy of a test.)

Atrial Fibrillation

- An analysis of *SCN5A*, *KCNQ1*, *MYL4*, and truncating *TTN* variants may be performed in all index patients in whom the diagnosis of familial (young is defined as age < 60 years) atrial fibrillation is established, based on examination of the patient's clinical history, family history, and ECG characteristics. (Some evidence and general agreement favor usefulness/efficacy of a test.)

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- Variant-specific genetic testing may be recommended for family members and appropriate relatives following the identification of the disease-causative variant. (Some evidence and general agreement favor usefulness/efficacy of a test.)
- Predictive genetic testing in related children may be considered in specific settings. (Some evidence and general agreement favor usefulness/efficacy of a test.)

Nielsen et al. (2020) published an expert consensus statement on behalf of the EHRA, HRS, APHRS, and LAHRS that addressed risk assessment in cardiac arrhythmias. This consensus recommends consideration of genetic testing for inherited arrhythmic disease that is associated with an increased risk of ventricular arrhythmia and sudden cardiac death; the authors emphasized that clinically meaningful testing should be guided by phenotype and pretest probability. Due to incomplete penetrance, the presence of a pathogenic variant alone is rarely sufficient to establish a diagnosis. Genetic testing may be informative for family members of a genotyped proband but is not recommended in the absence of a diagnostic ECG. The consensus statement further notes that testing for common genetic variants that are associated with atrial fibrillation has not demonstrated clinical utility; additional studies are needed to determine whether genetic information enhances atrial fibrillation risk prediction alongside clinical factors.

Cardiomyopathies

The Gasperetti et al. (2025) multicenter, retrospective, observational cohort study evaluated the clinical characteristics of and outcomes in patients who harbored pathogenic or likely pathogenic *DSP* variants; the authors used the DSP-ERADOS (Desmoplakin Specific Effort for a Rare Disease Outcome Study) Network, which includes 26 academic centers across nine countries. The objective was to characterize the natural history of *DSP*-associated cardiomyopathy and identify predictors of sustained ventricular arrhythmias and hospitalizations related to heart failure. Overall, 800 patients who had a single heterozygous *DSP* pathogenic or likely pathogenic variant, were alive at the first assessment, and had available follow-up were included. The mean age in the cohort was 40.3 ±17.5 years; 63.0% were female, 36.8% met 2010 Task Force Criteria for ARVC, 23.4% had nondilated left ventricular cardiomyopathy, 7.4% had DCM, and 32.5% did not meet the criteria for any of these phenotypes at baseline. Baseline testing availability was high for ECG (97.8%) and echocardiography (88.6%), with more limited availability of Holter monitoring (66.8%) and CMR imaging (68.9%). Over a median follow-up of 3.7 years (IQR, 1.4-7.1 years), sustained ventricular arrhythmia occurred in 139 patients (17.4%), corresponding to an incidence of 3.9% per year, and rapid sustained ventricular arrhythmia occurred in 69 patients (8.6%; 1.8% per year). Hospitalization related to heart failure occurred in 72 patients (9.0%; 1.8% per year), 38 (4.8%) underwent heart transplant, four (0.5%) received a left ventricular assist device, and 30 (3.8%) died. Among phenotype-negative patients, event rates were lower but not zero, with an overall ventricular arrhythmia incidence of 0.5% per year and an incidence of hospitalization related to heart failure of 0.3% per year. In multivariable analyses, independent predictors of sustained ventricular arrhythmia were female sex [adjusted HR (aHR), 1.547; $p = 0.025$], prior nonsustained ventricular tachycardia (aHR, 1.721; $p = 0.009$), prior sustained ventricular arrhythmia (aHR, 1.923; $p = 0.006$), and a left ventricular ejection fraction (LVEF) of ≤ 50% (aHR, 1.645; $p = 0.032$). For hospitalization related to heart failure, independent predictors were T-wave inversion in three or more ECG leads (aHR, 2.036; $p = 0.007$) and an LVEF of ≤ 50% (aHR, 3.879; $p < 0.001$). Myocardial injury episodes occurred in 70 patients (8.8%) and were associated with an increased subsequent risk of sustained ventricular arrhythmia (HR, 2.394; $p < 0.001$) and hospitalization related to heart failure (HR, 5.064; $p < 0.001$); the median time from myocardial injury to ventricular arrhythmia was 0.7 years (IQR, 0.5-4.6 years). Female patients experienced higher rates of palpitations, nonsustained ventricular tachycardia, greater T-wave inversion burden, and higher premature ventricular contraction burden, while male patients had a lower right ventricular ejection fraction. Female sex remained associated with higher ventricular arrhythmia risk in a multivariable analysis. The authors concluded that carriers of pathogenic or likely pathogenic *DSP* variants experience high rates of sustained ventricular arrhythmias and hospitalizations related to heart failure and demonstrate a distinct clinical phenotype that is characterized by ventricular ectopy, ECG abnormalities, left ventricular fibrosis, and systolic dysfunction, with uniquely higher arrhythmic risk in female individuals. They emphasized the prognostic importance of myocardial injury episodes and supported a gene-specific approach to risk stratification. This study's retrospective design, incomplete baseline imaging and Holter data, and lack of longitudinal assessment of phenotypic progression limit causal inference and long-term generalizability; prospective studies that include standardized follow-up are needed to validate these findings and refine gene-specific risk tools.

Hypertrophic Cardiomyopathy

The de Santana Santos et al. (2025) prospective cross-sectional study enrolled 200 adults from 152 families between June 2021 and August 2024 to characterize the genetic, clinical, and sociodemographic profile of participants with a prior HCM diagnosis or a family history of unconfirmed HCM and/or sudden cardiac death. Participants were consecutively referred by cardiologists; assignment was not randomized. Inclusion required an age of ≥ 18 years and echocardiographic or CMR imaging criteria that were consistent with HCM, defined as unexplained left ventricular wall thickness of ≥ 15 mm or ≥ 13 mm in those with a family history. Participants with hypertrophy that was attributable to other cardiac conditions

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were excluded. Of the total sample, 130 participants (65%; 95% CI, 57.9%-71.6%) met phenotypic criteria for HCM, and 70 had only a family history. The cohort was 58% male, with a median age of 52 years (range, 41-66 years). Genetic testing using a 19-gene next-generation sequencing panel that targeted sarcomeric and phenocopy-associated genes constituted the primary outcome, with pathogenic or likely pathogenic variants defining a positive genotype. Overall, 62 of the 200 participants (31%; 95% CI, 24.7%-37.9%) had pathogenic or likely pathogenic variants, 81 participants (40.5%) carried VUSs, and 57 (28.5%) had no reportable variants. Positive genotypes were more common in participants with a clinical HCM phenotype than in those with family history alone (37.7% vs 18.6%; p = 0.006). Among genetically positive participants, 77.4% (95% CI, 65.0%-87.1%) had sarcomeric variants, and 22.6% (95% CI, 12.9%-35.0%) had phenocopy-associated variants, most frequently involving *TTR*. The most common genes with pathogenic or likely pathogenic variants were *MYH7* [29 of 62 cases (46.77%)], *TTR* [13 cases (20.97%)], and *MYBPC3* [nine cases (14.52%)]. Participants with *TTR* variants were significantly older than those with sarcomeric variants, with median ages of 77 years vs 45 years, respectively (p < 0.001). Clinically, genotype-positive participants had greater interventricular septal thickness than genotype-negative participants, with a median of 17.7 mm vs 15.0 mm (p < 0.001); septal thickness of > 17 mm was identified as a strong predictor of a positive genetic result. A family history of sudden cardiac death was reported in 53% of the overall sample and was more frequent among genotype-positive participants than genotype-negative participants (68% vs 46%; p = 0.004). Palpitations were also more common in the genotype-positive group (71% vs 59%; p = 0.042), while dyspnea, syncope, and precordial pain did not differ significantly between groups. Left ventricular diastolic diameter and left atrial diameter were modestly smaller in genotype-positive participants (p = 0.030 and p = 0.029, respectively), while ejection fraction did not differ. The authors concluded that interventricular septal thickness of > 17 mm and a family history of sudden cardiac death were strong predictors of pathogenic or likely pathogenic genetic findings; this supports the integration of genetic testing into clinical evaluation and family management. Study limitations include its observational, cross-sectional design; lack of randomization and masking; absence of longitudinal follow-up to assess clinical outcomes or variant reclassification; and use of a predefined gene panel that excluded newly described genes and noncoding regions. Well-designed, longitudinal studies are needed to clarify long-term genotype-phenotype relationships.

The McBenedict et al. (2024) study was a systematic review, without meta-analysis, that evaluated the impact of genetic testing on diagnosis, management, and prognosis in HCM, as reported in studies that were published between January 2020 and May 2024. The 42 included studies involved adults with HCM who underwent genetic testing and had follow-up; these were predominantly observational cohort studies with no randomized comparisons, variable follow-up duration, and no masking. Sample sizes ranged from small, single-center cohorts to large, multicenter registries that enrolled thousands of individuals, with most populations enriched for men and individuals of European or Asian ancestry. However, several studies focused on other populations. Across studies, genetic testing identified pathogenic or likely pathogenic variants in approximately 26% to 55% of individuals, most commonly in *MYBPC3* and *MYH7*. Individuals with identified sarcomere mutations were generally younger at diagnosis; had more severe hypertrophy; had higher rates of arrhythmias, heart failure, and sudden cardiac death; and had more frequent family history of HCM. Quantitative associations included increased risks of cardiovascular death, all-cause death, or HCM-related morbid events in genotype-positive individuals. Several studies demonstrated that incorporating genetic data into existing sudden cardiac death risk models improved predictive performance, while genetic testing also enabled cascade testing that substantially increased identification of at-risk relatives. The authors concluded that genetic testing substantially improves diagnostic precision, risk stratification for sudden cardiac death, and individualization of management in HCM, including informing surveillance intensity, implantable cardioverter-defibrillator consideration, and family screening. However, confidence in these findings is limited by the observational nature of the included studies; absence of randomized or controlled comparisons; and heterogeneity in study designs, populations, genetic panels, and outcome definitions. Across studies, there was inconsistent reporting of effect estimates and CIs and variable follow-up durations. Additional limitations include potential selection bias toward individuals who were referred for genetic testing and underrepresentation of certain demographic groups. Well-designed, comparative studies that include standardized outcomes and longer follow-up are needed to define the clinical impact of genetic testing on individuals' management and outcomes. A publication by Hathaway et al. (2021), previously discussed in this policy, was included in this systematic review.

Topriceanu et al. (2024) conducted a systematic review and meta-analysis that examined the prevalence and penetrance of pathogenic or likely pathogenic sarcomeric variants; the authors compared findings from family-ascertained and clinically ascertained cohorts with those from population-based studies that included genetic and cardiac imaging data. Additional meta-analyses of longitudinal studies were performed to characterize progression from subclinical disease to clinically diagnosed HCM. Following a systematic literature search, 455 full-text publications were assessed. Among family and clinical cohorts, sarcomeric variants were identified in 34% of individuals with HCM. In nonproband relatives who carried pathogenic/likely pathogenic variants that were identified through cascade screening, penetrance across all genes was 57% (95% CI, 52%-63%), with a mean age at diagnosis of 38 years. Penetrance varied by gene, ranging from approximately 32% for *MYL3* to 55% for *MYBPC3*; 60% for *TNNT2* and *TNNI3*; and 65% for *MYH7*. Population-based studies showed that pathogenic/likely pathogenic sarcomeric variants are present in the general population at a low prevalence (< 1%) and that the proportion of variant carriers with HCM was lower, ranging from 0% to 18% depending on

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the cohort. Across longitudinal studies, pooled phenotypic conversion was 15% over a mean follow-up of 8 years, with short-term conversion rates for *MYBPC3* and *MYH7* of 12% and 23%, respectively. The authors concluded that the likelihood of developing clinically overt HCM is significantly higher in affected cohorts and their families than in the general population and that penetrance is highly variable and likely influenced by genetic and environmental modifiers. They emphasized the need for high-quality, longitudinal studies to better define determinants of disease progression and clarify HCM pathogenesis. The publications by Alfares et al. (2015), Loar et al. (2015), and Gruner et al. (2013), which were previously discussed in this policy, were included in this systematic review and meta-analysis.

Nielsen et al. (2023) examined disease expression and penetrance among relatives of participants who carried pathogenic or likely pathogenic variants in established HCM genes. This multicenter, longitudinal cohort study included 453 unrelated participants with HCM who underwent clinical and genetic evaluation. The analysis also incorporated 757 relatives of variant-positive index participants, all of whom received analogous assessments. The outcomes of interest included disease penetrance, clinical expression, and incidence of other major adverse cardiac events among pathogenic/likely pathogenic variant carriers. Among index participants, 183 of 453 (40%) carried a pathogenic/likely pathogenic variant. Of the relatives, 407 of 757 (54%) were variant carriers, with an HCM penetrance of 39% (160 of 407). The age at diagnosis did not differ significantly between affected index participants and relatives (43 ±18 years vs 46 ±15 years; p = 0.11). Over a median follow-up of 8 years, no significant differences were observed in clinical presentation or major adverse cardiac event incidence between groups. Limitations of this study include its recruitment from only tertiary referral hospitals (including one transplant center), which may have enriched the cohort for more severe disease. The younger age of unaffected carriers potentially underestimates age-dependent penetrance. Additionally, 16% of invited relatives declined participation, which introduced possible selection bias. Despite these limitations, the authors concluded that HCM expression and major adverse cardiac event risk are comparable between affected individuals and relatives who carry HCM-associated pathogenic/likely pathogenic variants; this supports the clinical value of cascade genetic screening and longitudinal follow-up in genotype-positive family members.

Cirino et al. (2022) conducted a systematic review and meta-analysis to evaluate (1) the use of genetic counseling and testing in individuals with HCM and their at-risk family members and (2) the associated patient-reported outcomes (PROs). The analysis included 48 studies (47 observational and one randomized). The genetic testing uptake was 57% among probands (95% CI, 40%-73%) and 61% among at-risk family members (95% CI, 45%-75%). The uptake of cardiac screening was 58% (95% CI, 40%-73%) and of combined cardiac and genetic screening was 69% (95% CI, 43%-87%). Family members of probands with positive test results were significantly more likely to pursue cascade screening than those with negative results (odds ratio, 3.17; 95% CI, 2.12-4.76). The uptake of genetic counseling ranged from 37% to 84% among probands and family members. Differences in PROs between individuals with positive vs negative results were generally small, although some studies reported worse psychological outcomes following positive results. Genetic counseling was consistently associated with high satisfaction, increased perceived control and empowerment, and reduced anxiety. The authors concluded that PROs following genetic testing are variable but that genetic counseling is linked to favorable outcomes; they highlighted the need for further research on decision-making, strategies to improve cascade screening, psychological impacts of testing, and standardized outcome reporting across cardiovascular genetics programs. A publication by Murphy et al. (2016), previously discussed in this policy, was included in this systematic review and meta-analysis.

Christian et al. (2022) performed a systematic review and meta-analysis that evaluated the diagnostic validity and clinical utility of genetic testing in individuals with HCM and at-risk relatives. The review included 132 studies that were published through March 2020, spanning 25 years; 80 reported variant detection rates, 44 examined genotype-phenotype associations, and 51 evaluated disease penetrance. Prespecified sensitivity and subgroup analyses assessed sarcomere genes, age groups, family history, proband inclusion, variant pathogenicity, and classification methods. Detection rates were higher in pediatric cohorts than adult cohorts (56% vs 42%; p = 0.01) and among adults with a family history compared with sporadic cases (59% vs 33%; p = 0.005). Use of contemporary variant interpretation standards reduced detection rates from 42% to 33% (p = 0.0001). Genotype-positive adults developed disease earlier than genotype-negative individuals (mean difference, 8.3 years; p < 0.0001), with similar differences observed for *MYH7* vs *MYBPC2* variants and in individuals who carried multiple variants (8.2 years, p < 0.0001 and 7.0 years, p < 0.0002, respectively). Overall disease penetrance in adults was 62%, with higher estimates when probands were included (73% vs 55%; p = 0.003). Although heterogeneity in the study design and outcomes reporting limited some analyses, this meta-analysis suggests key patterns in detection rates, penetrance, and genotype-phenotype associations, which may support the clinical utility of genetic testing for HCM. The publications by Mazzarotto et al. (2019), Restrepo-Cordoba et al. (2017), Murphy et al. (2016), Rubattu et al. (2016), Alfares et al. (2015), Loar et al. (2015), Gruner et al. (2013), Ingles et al. (2013), Zou et al. (2013), Michels et al. (2009), Olivotto et al. (2008), Richard et al. (2003), Van Driest et al. (2003), Niimura et al. (1998), Charron et al. (1997), and Watkins et al. (1995), previously discussed in this policy, were included in this systematic review and meta-analysis.

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Arrhythmogenic Cardiomyopathy, Including Arrhythmogenic Right Ventricular Cardiomyopathy

The Hoogendoorn et al. (2025) retrospective observational study evaluated whether baseline 12-lead ECG findings could identify atypical right ventricular involvement suggestive of alternative underlying etiologies in patients who fulfilled the 2010 Task Force Criteria for definite ARVC and presented with sustained ventricular tachycardia. Using a national ACM registry, the investigators included 159 patients who met the Task Force Criteria, experienced sustained ventricular tachycardia, underwent genetic testing, and had a nonpaced ECG available after the arrhythmic event. The cohort included 122 patients with an ARVC-related pathogenic or likely pathogenic variant in *PKP2*, *PLN*, *DSG-2*, *LMNA*, and/or *DSP*. ECGs were analyzed, blinded to clinical and genetic data, with atypical right ventricular involvement defined by a PR prolongation of ≥ 220 ms and/or a surface area of the maximum R wave in leads V1 to V3 of ≥ 1.65 mm², including predefined atypical morphologies. Genetic variant–negative cases and variant-positive cases with atypical ECGs were subsequently reviewed by a multidisciplinary expert panel to classify the most likely underlying etiology, based on all available clinical, imaging, and follow-up data. An atypical right ventricular involvement ECG was present in 19 of 159 patients (12%), occurring more frequently in variant-negative than variant-positive patients (22% vs 9%; p = 0.038). Among the 37 variant-negative patients, 17 (46%) were classified by expert consensus as having a different etiology such as myocarditis, cardiac sarcoidosis, ischemic cardiomyopathy, or laminopathy, and all eight variant-negative patients with an atypical ECG were classified as having a different etiology compared with nine of 29 without an atypical ECG (p = 0.001). In this subgroup, the atypical ECG showed 47% sensitivity, 100% specificity, a positive predictive value of 100%, and a negative predictive value of 69% for identifying a non-ARVC etiology. Among variant-positive patients, those with an atypical ECG were older and more frequently carried the *PLN* p.Arg14del variant (46% vs 15%; p = 0.01), had more left ventricular dysfunction (55% vs 19%; p = 0.016), and experienced substantially worse outcomes over a median 12-year follow-up, with heart failure in 73% vs 24% (p = 0.002) and death or heart transplant in 64% vs 19% (p = 0.003); these associations persisted after excluding *PLN* carriers. The authors concluded that an atypical right ventricular involvement ECG should prompt suspicion of an alternative underlying etiology in variant-negative individuals who fulfill the Task Force Criteria and may identify a high-risk subgroup among variant-positive individuals. The findings are limited by the study's retrospective design; reliance on expert adjudication, without systematic confirmatory testing for alternative diagnoses; small numbers of patients with atypical ECGs; lack of randomization or masking beyond ECG analysis; and potential confounding by age and disease severity, all of which underscore the need for prospective comparative studies with standardized diagnostic protocols.

The Chen et al. (2025) multicenter, observational cohort study pooled genetic and clinical data from 11 centers to define the phenotypic expression, natural history, and outcomes of ARVC that is attributable to pathogenic or likely pathogenic *DSG2* or *DSC2* variants. The cohort included 271 participants; 254 carried *DSG2* variants, 15 carried *DSC2* variants, and two carried both. Overall, 200 met definite ARVC criteria. The median age at enrollment was 38 years, 62.7% were male, and 48.3% were of European ancestry. Multiple variants were identified in 78 participants (28.8%). The median age at ARVC diagnosis was 35 years, with 21.5% diagnosed before age 20 years. The clinical presentation was predominantly right ventricular or biventricular, with isolated left ventricular disease being rare. Of the 81 participants with complete biventricular functional data at presentation, 35.8% had isolated right ventricular dysfunction, and 19.8% had biventricular dysfunction. Late gadolinium enhancement on CMR imaging was present in 71.9% of those imaged and typically involved the right ventricle alone or both ventricles. During the disease course, 41 of 200 diagnosed participants (20.5%) experienced cardiac death before age 65 years, which was most commonly related to heart transplant or end-stage heart failure. Carriers of multiple *DSG2*/*DSC2* variants had substantially earlier disease onset and more severe disease than single-variant carriers. They were more likely to be diagnosed with ARVC (96.2% vs 64.8%), were younger at diagnosis (median age, 33 vs 42 years), and had higher rates of left ventricular systolic dysfunction, right ventricular dilation, advanced New York Heart Association class, heart transplant, malignant ventricular arrhythmias, and end-stage heart failure. During follow-up, malignant ventricular arrhythmias occurred in 36.2% of carriers, and end-stage heart failure occurred in 13.3%, with multiple-variant status being strongly associated with both outcomes; multiple variants were linked to higher risks of malignant ventricular arrhythmias and end-stage heart failure, and an LVEF of < 50% independently predicted heart failure progression. Among single-variant carriers, intense physical exercise was associated with earlier disease onset and more pronounced electrical and structural right ventricular abnormalities, whereas no similar modifying effect was observed in multiple-variant carriers; exercise did not significantly affect end-stage heart failure risk in either group. The authors concluded that *DSG2*/*DSC2*-related ARVC is characterized by right-dominant or biventricular involvement; a high prevalence of multiple-variant carriers; and a substantial burden of heart failure, with multiple variants conferring earlier penetrance and worse outcomes. The study's findings are limited by the retrospective design, missing baseline data, qualitative exercise assessment, and incomplete follow-up, but they suggest that genetic subclassification, particularly identification of multiple variants, is critical for risk stratification and interpretation of prognosis.

The Muller et al. (2025) multicenter, observational cohort study examined genotype-specific disease progression and ventricular arrhythmia risk in relatives of probands who were carrying a pathogenic or likely pathogenic *PKP2* variant, with the aim of developing an evidence-based, longitudinal family screening algorithm for ARVC. The investigators included

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295 individuals from 145 families that were identified through a national ACM registry and the Johns Hopkins ARVC Registry; individuals had undergone baseline evaluation that was sufficient to adjudicate a diagnosis using the 2010 Task Force Criteria. The baseline assessment consisted of a 12-lead ECG, Holter monitoring for at least 24 hours, and cardiac imaging, with follow-up testing performed at the discretion of treating clinicians. At enrollment, the median age of individuals was 30.9 years; 122 (41%) were male, and 205 (69%) were first-degree relatives of the proband. Definite ARVC was identified in 110 individuals (37%) at baseline; 117 individuals were classified as genotype positive/phenotype negative, and 68 met the Task Force Criteria for borderline ARVC. The distribution of individuals by degree of relationship with the proband differed significantly by baseline phenotype ($p < 0.001$), with siblings comprising 46.4% of those with definite ARVC, 18.8% of the genotype-positive/phenotype-negative cohort, and 23.9% of the borderline ARVC cohort; second- and third-degree relatives together accounted for 36.8% of the genotype-positive/phenotype-negative group and 41.8% of the borderline ARVC group vs 17.3% of the individuals with definite ARVC. During the follow-up period (median, 8.5 years), 62 of 185 individuals (34%) without definite ARVC at baseline progressed to definite ARVC, with a median time to onset of 5.3 years. Sustained ventricular arrhythmias occurred in 35 of 295 individuals (12%), corresponding to an annual incidence of 1.4%, and all events occurred after individuals had fulfilled definite ARVC diagnostic criteria. Among the 185 individuals without definite ARVC at baseline, only three (1.6%) developed a ventricular arrhythmia during follow-up, and in all three cases, the arrhythmia occurred more than 6 years after definite ARVC diagnosis. Multistate modeling demonstrated that individuals with borderline ARVC progressed approximately five times faster to definite ARVC than genotype-positive/phenotype-negative individuals. Cox frailty regression identified the age range of 20 to 40 years as a significant predictor of progression compared with those aged 40 years or older (HR, 2.33), with female sex also associated with higher risk (HR, 2.38). Being a sibling of the proband was not independently associated with progression after adjustment for baseline phenotype; this indicates that the observed overrepresentation of siblings among those with definite ARVC may reflect ascertainment bias rather than differential biological risk. The authors concluded that a genotype-specific longitudinal screening strategy that integrates baseline phenotype, age, and symptoms can support a diagnosis of definite ARVC years before an index ventricular arrhythmia event while allowing less intensive surveillance in lower-risk relatives. These findings are limited by the study's observational design, lack of standardized follow-up, possible overrepresentation of first-degree relatives in the definite ARVC group, limited power to assess predictors of ventricular arrhythmia, and incomplete data on potential modifiers such as exercise exposure, which together constrain the generalizability of progression estimates for distant relatives and across clinical settings.

The García-Cano et al. (2024) single-center, prospective cohort study evaluated whether genetic testing findings had prognostic significance in participants who were diagnosed with left dominant ACM or biventricular ACM. From January 2010 through December 2020, 77 participants who met Sen-Chowdhry diagnostic criteria and had characteristic CMR imaging findings were recruited and followed up at a tertiary referral center. All participants underwent ECG, echocardiography, Holter monitoring, CMR imaging, and next-generation sequencing using a cardiomyopathy and arrhythmia gene panel; pathogenic variants, likely pathogenic variants, and selected VUSs with familial cosegregation were considered positive. The cohort had a mean age of 54.5 ±13.7 years, and 64.9% of participants were male. A positive genetic result was identified in 41 participants (53.2%), with *DSP* variants being most frequent (16.9%); 10.4% carried multiple variants. The mean LVEF at diagnosis was 45.8% ±13.1%, and left ventricular dilation was present in 51.9%, with no differences in ventricular volumes or systolic function according to genetic status. Fibrosis was present on CMR imaging in all participants; those with positive genetics had a higher number of left ventricular segments with late gadolinium enhancement (11.0 ±5.4 vs 8.7 ±4.6; $p = 0.043$), while the presence and extent of fatty infiltration did not differ significantly ($p = 0.144$). Right ventricular involvement occurred in 28.6% of the cohort, without differences by genetic status. Over a median follow-up of 3.24 years, with complete ascertainment, 23 participants (29.9%) experienced major adverse cardiovascular events, including sustained ventricular arrhythmias (19.5%), sudden death (3.9%), aborted sudden death (5.2%), and heart transplant (1.3%). The occurrence of major adverse cardiovascular events did not differ between those with positive or negative genetic test results (29.3% vs 30.6%; $p = 0.902$) and neither did individual event types, need for cardioverter-defibrillator implantation (45.5% overall; $p = 0.532$), or appropriate therapy by the cardioverter-defibrillator device ($p = 0.217$). The authors concluded that although genetic variants were identified in just over half of participants and were associated with greater myocardial fibrosis burden, genetic test positivity was not associated with worse clinical outcomes during follow-up. The findings are limited by the observational design, relatively small sample size, absence of randomization or blinding, and potential incomplete genetic characterization due to evolving panels over the long enrollment period.

The Bermudez-Jimenez et al. (2024) multicenter, longitudinal cohort study evaluated the phenotype and clinical outcomes of ACM that was attributable to *DES* variants; 82 participants from 16 families across 10 referral centers were enrolled, including probands and genetically affected relatives. Eligible participants met 2020 Padua criteria for a definitive or borderline diagnosis of ACM or were silent carriers, with variant pathogenicity assessed using ACMG guidelines. The median age at diagnosis was 36 years, 54.9% of participants were male, and 76.5% were identified through cascade screening. Before clinical evaluation, 11 participants had sudden cardiac death, heart failure, or heart transplant, which left 68 participants for phenotypic and outcome analyses. Among the 68 clinically evaluated participants, 59 (86%)

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presented with signs of cardiomyopathy, most commonly with left ventricular–dominant (50%) or biventricular (33.8%) involvement; isolated right ventricular disease was rare (2.9%). The mean LVEF was 50.7% ±13%, and late gadolinium enhancement was present in 36 of the 53 participants who were undergoing CMR imaging, with a subepicardial ring-like pattern in 17 participants (47%) with enhancement. During a median follow-up period of 6.73 years, 15 of the 68 clinically evaluated participants (22%) experienced the composite end point [sustained ventricular tachycardia (n = 6), sudden cardiac death (n = 2), aborted sudden cardiac death (n = 1), heart failure death (n = 3), or heart transplant (n = 3)]. In the full cohort of 82 participants, male sex (p = 0.004), presence of nonsustained ventricular tachycardia on ambulatory monitoring (p = 0.017), and an LVEF of ≤ 50% (p = 0.012) were associated with an increased risk of the composite outcome, while late gadolinium enhancement was not independently associated. A survival analysis showed that male participants with *DES* variants had similar outcomes to historical cohorts with *LMNA* truncating and *FLNC* truncating variants, while female participants with *DES* variants had better outcomes than female participants with *LMNA* truncating variants. The authors concluded that *DES*-related ACM is characterized by high penetrance, predominant left ventricular or biventricular involvement, and a substantial risk of malignant ventricular arrhythmias and advanced heart failure, particularly in male individuals, with outcomes comparable to those in other high-risk genetic ACM subtypes. Important limitations of this study include the observational design, incomplete phenotypic data for participants whose first manifestation was sudden death, lack of randomization or a contemporary control group, potential lead time and selection biases related to proband-driven ascertainment, incomplete follow-up, and limited assessment of treatment effects. The small cohort size and event numbers constrain power for multivariable risk modeling and limit generalizability. Well-designed, comparative studies are needed.

The Gasperetti et al. (2024) retrospective, observational cohort study examined long-term arrhythmic outcomes and the performance of the ARVC Risk Calculator in patients with likely pathogenic or pathogenic *DES* variants who fulfilled the definite 2010 Task Force Criteria for ARVC. Overall, 252 patients (35.3% male; 94.4% of European ancestry) were enrolled from registries across 20 academic institutions, with a mean age of 39.6 ±16.9 years at Task Force Criteria fulfillment. Most patients (81.0%) had no history of sustained ventricular arrhythmia at diagnosis and were assigned to a primary prevention cohort. Left ventricular involvement, defined as late gadolinium enhancement on CMR imaging and/or an LVEF of < 50%, was present in 77.0%. The primary outcome was first sustained ventricular arrhythmia after diagnosis, defined as sustained ventricular tachycardia of ≥ 30 seconds, ventricular fibrillation, sudden cardiac arrest, or appropriate implantable cardioverter-defibrillator therapy. Over a median follow-up of 44.5 months (IQR, 19.6-78.3 months), 94 patients (37.3%) experienced sustained ventricular arrhythmias, corresponding to an annualized 5-year event rate of 7.6% (IQR, 6.2%-9.2%). In the primary prevention cohort, 67 of 204 patients (32.8%) developed sustained ventricular arrhythmias, with an annualized 5-year rate of 7.7% (IQR, 6.1%-9.4%). Ventricular arrhythmias occurred more frequently in those with left ventricular involvement than those without, both in the overall cohort (39.7% vs 29.3%; log-rank p = 0.0239) and in the primary prevention cohort (35.9% vs 22.9%; log-rank p = 0.0133). In univariable Cox regression, left ventricular involvement (HR, 2.121; 95% CI, 1.088-04.138; p = 0.027), higher premature ventricular contraction burden (HR, 1.189 per log increase; 95% CI, 1.034-1.368; p = 0.015), and history of nonsustained ventricular tachycardia (HR, 2.629; 95% CI, 1.655-4.176; p < 0.001) were associated with sustained ventricular arrhythmia, while age (p = 0.723) and male sex (p = 0.200) were not. In a multivariable analysis, nonsustained ventricular tachycardia remained associated with sustained ventricular arrhythmias (aHR, 2.097; 95% CI, 1.274-3.450; p = 0.004). When components of left ventricular involvement were modeled separately, a lower LVEF (aHR, 0.977; 95% CI, 0.956-0.998; p = 0.028) and nonsustained ventricular tachycardia (aHR, 2.236; 95% CI, 1.364-3.663; p = 0.001) were associated with events, while left ventricular late gadolinium enhancement was not. Among the 204 patients in the primary prevention cohort, the median predicted 5-year ventricular arrhythmia risk by the ARVC Risk Calculator was 15.4% (IQR, 8.3%-25.0%), although observed arrhythmic risk discrimination was poor. Performance was particularly limited in those with left ventricular involvement, with a C-statistic of 0.558 (95% CI, 0.556-0.560), whereas discrimination was better in patients without left ventricular involvement (C-statistic, 0.756; 95% CI, 0.702-0.810); however, risk tended to be underestimated. During follow-up, 18.6% experienced heart failure–related hospitalizations, 8.7% underwent heart transplant, and overall mortality was 2.8%. At the last follow-up, 69.4% had an implantable cardioverter-defibrillator. The authors concluded that patients with *DES*-associated ACM who fulfill Task Force Criteria have a high risk of sustained ventricular arrhythmias, including in the absence of prior arrhythmic events, and that the ARVC Risk Calculator performs poorly in this genotype, especially when left ventricular involvement is present. The findings are limited by the study's retrospective design, lack of nonsustained ventricular tachycardia burden data, categorical assessment of late gadolinium enhancement, and the focus on a phenotype-defined cohort, indicating that gene-specific, prospective risk stratification approaches may be needed.

Bariani et al. (2022) conducted a systematic review to characterize the genetic background and clinical features of arrhythmogenic left ventricular cardiomyopathy (ALVC). The authors included 31 original studies that reported individual-level genetic, clinical, ECG, and imaging data for individuals who were diagnosed with ALVC. Across the included studies, data were derived predominantly from single-center, observational reports, case series, and case reports. In total, the review synthesized detailed information on genotyped individuals with ALVC, with *DSP* variants reported in 65% of included studies and representing approximately half of reported cases, followed by *FLNC*, *PLN*, *DES*; rare reports

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involved *LMNA*, *DSG2*, or *PKP2*. Across pooled individual-level data, ECG abnormalities were reported in 58% of individuals, most commonly low QRS voltages and inferolateral T-wave inversion, which occurred in 26% and 36% of cases, respectively. Left ventricular dilation or systolic dysfunction on echocardiography was reported in 61% of individuals, and subepicardial or ring-like left ventricular late gadolinium enhancement was identified on CMR imaging in 79% of cases. Major ventricular arrhythmias, including sustained ventricular tachycardia, ventricular fibrillation, syncope, and sudden death, occurred in 26% of individuals, and 29% underwent implantable cardioverter-defibrillator implantation. Heart failure symptoms were reported in 6% of cases, while myocarditis-like "hot phase" episodes, which were characterized by chest pain, troponin release, and ECG changes, with normal coronary arteries, were reported in 15% of individuals. The authors concluded that *DSP* is the most frequently implicated gene in ALVC and that ALVC is characterized by substantial electrical instability and a non-negligible burden of myocarditis-like presentations. The findings are limited by the reliance on small, heterogeneous observational studies and case reports; inconsistent reporting of clinical variables and follow-up; and lack of comparative or controlled data, all of which collectively limit confidence in the precision and generalizability of the summarized estimates.

Dilated Cardiomyopathy

The Stroeks et al. (2025) multicenter, observational, longitudinal cohort study evaluated genotype-phenotype associations and their prognostic value in participants with genotype-positive DCM. The objective was to characterize genotype-specific clinical features, assess whether phenotype-based clustering reflects underlying genotype, and compare genotype-first vs phenotype-first approaches for outcome prediction. The study enrolled 534 participants who were aged over 16 years with DCM and recruited from inherited cardiomyopathy and heart failure units across five tertiary centers. All participants met the diagnostic criteria for DCM, with an LVEF of < 50% and no alternative structural or ischemic cause. Genetic testing was performed using targeted next-generation sequencing panels, which covered at least 19 established DCM-associated genes, with variant classification according to ACMG criteria. Participants underwent standardized baseline clinical evaluation and longitudinal follow-up, with a median follow-up duration of 7.6 years (IQR, 4.2-13.3 years). The outcomes included a composite primary end point of all-cause mortality, heart failure hospitalization, heart transplant, or malignant ventricular arrhythmia, with secondary end points of heart failure–related events and arrhythmic events alone. Genotype-first analyses identified significant genotype-phenotype associations for 10 genes. *LMNA* and *PLN* variants were characterized by higher rates of atrial fibrillation, conduction disease, nonsustained ventricular tachycardia, atrioventricular block, and low peripheral ECG voltages, whereas *BAG3*, *TNNT2*, *DMD*, and *TTN* variants were associated with larger cardiac volumes and a lower LVEF, often in the absence of baseline arrhythmias. Phenotype-first hierarchical clustering, using 17 clinical variables, identified four phenoclusters, which were defined by age at diagnosis, LVEF, ventricular dimensions, arrhythmias, and functional class, but there was minimal concordance between phenoclusters and genotype. During follow-up, 175 participants (33%) experienced the composite primary end point; 112 (21%) experienced heart failure–related events, and 67 (13%) experienced malignant ventricular arrhythmias. In genotype-first survival analyses, *LMNA*, *FLNC*, and *BAG3* variants were associated with the highest long-term risk for the composite outcome, while *BAG3*, *LMNA*, and *RBM20* conferred the highest risk for heart failure–related events; *LMNA*, *DSP*, *FLNC*, and *BAG3* had the highest risk for malignant ventricular arrhythmias. These associations remained after adjustment for age, sex, and baseline LVEF, with *TTN* used as the reference genotype. Phenotype-first analyses showed that phenoclusters with severely reduced LVEF had worse outcomes, but genotype explained a substantially greater proportion of prognostic information than phenocluster, LVEF, age, and sex. The authors concluded that genotype is the strongest predictor of adverse outcomes in genetic DCM and that phenotype-based clustering alone does not reliably stratify risk or reflect genetic architecture. Limitations include the retrospective, observational design; incomplete availability of some clinically relevant variables such as CMR imaging parameters; reliance on baseline arrhythmia assessment; and small sample sizes for some rare genotypes. Overall, the findings indicate that genotype-based risk stratification is more accurate than a phenotype-first approach and support the need for gene-specific risk prediction models; the findings are limited by the lack of randomization and incomplete phenotypic data, and well-designed, genotype-focused studies that use comprehensive phenotyping are needed.

The Mora-Ayestarán et al. (2025) multicenter, retrospective observational cohort study evaluated whether patients with DCM who were carrying pathogenic or likely pathogenic variants in high-risk arrhythmic genes experienced a higher burden of advanced heart failure than other genotypic groups. The study included 1,203 consecutively recruited genotyped patients with nonischemic DCM from 19 inherited cardiac disease and heart failure centers between 2015 and 2022; all patients were older than 15 years at diagnosis. Genetic testing was performed using next-generation sequencing panels that covered more than 50 cardiomyopathy-associated genes, without preselection based on phenotype or family history. Patients were classified into four groups: high-risk arrhythmic genotypes (*LMNA*, *FLNC*, *PLN*, *TMEM43*, and *RBM20* and the desmosomal genes *DSG2*, *DSC2*, and *PKP2*; n = 185); *TTN* genotypes (n = 193); other DCM-associated genotypes (n = 134); and genotype-negative patients, including those with VUSs (n = 691). The primary end point was a composite of advanced heart failure events that consisted of ventricular assist device implantation, heart transplant, or advanced heart failure–related mortality; the secondary end point was a composite of malignant ventricular arrhythmias, including sudden cardiac death, aborted sudden cardiac death, sustained ventricular tachycardia, or appropriate

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implantable cardioverter-defibrillator shocks. The median follow-up was 5.7 years (IQR, 2.9-9.1 years). Advanced heart failure events occurred in 45 patients (24.3%) in the high-risk arrhythmic genotype group compared with 25 (13.0%) in the *TTN* group, 25 (18.7%) in the other genotype group, and 70 (10.1%) in the genotype-negative/VUS group, corresponding to an HR of 1.85 (95% CI, 1.31-2.61) for high-risk arrhythmic genotypes vs other groups. Malignant ventricular arrhythmias occurred in 55 patients (29.7%) with high-risk arrhythmic genotypes compared with 24 (12.4%), 21 (15.7%), and 82 (11.9%) in the *TTN*, other genotype, and genotype-negative/VUS groups, respectively, with an HR of 2.52 (95% CI, 1.81-3.51). In a multivariate Cox regression analysis that was adjusted for genotype, late gadolinium enhancement, LVEF, and New York Heart Association class, a high-risk arrhythmic genotype was the strongest independent predictor of advanced heart failure (HR, 4.01; 95% CI, 1.73-9.34; p = 0.001), while a high-risk arrhythmic genotype (HR, 3.41; 95% CI, 1.87-6.21) and late gadolinium enhancement (HR, 3.57; 95% CI, 2.15-5.91) independently predicted malignant ventricular arrhythmias. The authors concluded that individuals with DCM carrying high-risk arrhythmic genotypes experience substantially more advanced heart failure complications in addition to malignant ventricular arrhythmias; this supports the need for a broader, genotype-informed therapeutic approach beyond sudden death prevention alone. The findings are limited by the retrospective, observational design; potential baseline treatment differences; lack of serial LVEF measurements to assess temporal changes; and possible limited generalizability, given recruitment from specialized inherited cardiac disease and heart failure centers.

The Johnson et al. (2025) international, multicenter, retrospective, observational study examined determinants of disease onset in families with titin truncating variant (*TTN*tv)–associated DCM. The investigators analyzed 3,158 patients from 1,043 families who were evaluated at 41 centers in 12 countries between 1993 and 2023; shared frailty survival models that were adjusted for sex and family relatedness were used to assess penetrance, and multivariable mixed-effects logistic regression was used to evaluate associations between clinical factors and DCM. Among 3,106 patients in the primary cohort with clinically reportable *TTN*tvs, *TTN*tv-positive patients had a markedly higher lifetime risk of DCM compared with *TTN*tv-negative relatives (HR, 21.21; 95% CI, 14.80-30.39). The median age at DCM diagnosis was 48 years, with earlier onset in male patients than female patients; cumulative incidence analyses estimated that 88% of *TTN*tv-positive patients (93% of male patients and 79% of female patients) developed DCM by 70 years of age. Penetrance analyses showed no statistically significant differences by truncating variant type, splice-site class, predicted splicing consequence, or titin domain location when variants were in constitutively expressed exons, indicating similar genetic risk across these categories. In contrast, individual clinical context strongly modified disease expression. In adjusted logistic regression models, the presence of one or more clinical risk factors prior to diagnosis was associated with substantially increased odds of DCM (odds ratio, 3.41; 95% CI, 2.06-5.64), with atrial fibrillation conferring approximately two-fold higher odds of DCM (odds ratio, 2.05; 95% CI, 1.27-3.32). Risk factor prevalence increased with age, yet associations with DCM were strongest in patients with disease onset before age 30 years (odds ratio, 4.75; 95% CI, 2.35-9.60). Conversely, receipt of β-adrenergic receptor or renin-angiotensin system–blocking therapy prior to overt DCM was associated with an 87% reduction in the odds of developing DCM (odds ratio, 0.13; 95% CI, 0.08-0.23), and moderate or high habitual exercise was associated with lower odds of DCM compared with sedentary behavior, particularly in female patients. The authors concluded that although lifetime penetrance of *TTN*tv-associated familial DCM is high, age at onset is strongly influenced by modifiable clinical factors and preventive therapy. However, the study used a retrospective, observational design, the population was predominantly of European ancestry, and randomized intervention was lacking, all of which limit causal inference. Prospective studies are needed to validate prevention strategies.

The Dal Ferro et al. (2024) single-center, retrospective, observational study evaluated whether a DCM-causing genetic background influences long-term left ventricular remodeling and clinical outcomes after cardiac resynchronization therapy (CRT) in patients with nonischemic DCM, severe left ventricular dysfunction, and left bundle-branch block. The cohort comprised 74 patients who were undergoing de novo CRT between 2008 and 2018 and had available genetic testing results. Of them, 25 were classified as having genetically determined disease, based on carriage of pathogenic or likely pathogenic variants in validated DCM-causing genes and/or documented familial DCM; 49 were classified as having idiopathic DCM, without identified pathogenic variants or a family history. Baseline characteristics were largely comparable between groups, including left ventricular volumes and ejection fraction, medical therapy, and CRT procedural features, although QRS duration was longer in the idiopathic group (median, 175 ms vs 161 ms). The primary outcome assessed left ventricular reverse remodeling at 24 to 48 months, which was measured by the relative change in ejection fraction and end-systolic volume and by the prevalence of super response; super response was defined as an ejection fraction of greater than 50%. Among the 65 patients who were evaluable at 2 years, both groups experienced improvement from baseline, but the magnitude differed markedly. The median ejection fraction at follow-up was 44% in idiopathic disease vs 29% in genetically determined disease (p = 0.009), with greater relative improvement in ejection fraction (from 27% to 44% vs 25% to 29%) and greater relative reductions in end-systolic volume (-50% vs -11%; p = 0.004) and end-diastolic volume (-39% vs -12%; p = 0.038) in the idiopathic group. Super response occurred in 27% of patients with idiopathic disease and in 5% with genetically determined disease (p = 0.025). After adjustment for baseline ejection fraction, idiopathic disease was associated with a 12-point greater median increase in ejection fraction (95% CI,

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7.8-22 points). The secondary composite outcome of heart failure–related death, heart transplant, or left ventricular assist device implantation was assessed over a median follow-up of 55 to 56 months. This outcome was observed more frequently in genetically determined disease [13 of 25 (52%)] than in idiopathic disease [12 of 49 (24%)], which was a statistically significant difference (p = 0.021). The genetically determined group had worse event-free survival; this unfavorable trend persisted after exclusion of super responders. Among genotypes, *LMNA* variant carriers accounted for a disproportionate number of adverse outcomes, although gene-specific effect estimates were not reported. All super responders remained free of heart failure events during follow-up. The authors concluded that genetic testing meaningfully contributes to prognostic stratification in individuals with DCM who are undergoing CRT, with nonhereditary idiopathic disease associated with greater reverse remodeling, higher prevalence of super response, and lower rates of advanced heart failure outcomes. The findings are limited by the retrospective design, single-center setting, small sample size, lack of randomization or masking, limited power for genotype-specific analyses, and moderate attrition prior to the remodeling assessment, which together constrain the certainty and generalizability of the conclusions and underscore the need for larger, comparative studies.

The Cabrera-Romero et al. (2024) retrospective, multicenter cohort study evaluated 779 genotype-positive relatives of patients with DCM who did not meet the diagnostic criteria for DCM at baseline; patients were followed up at 25 centers, with serial ECG and cardiac imaging, over a median follow-up of 37.1 months. Cardiac conduction abnormalities were explicitly captured in the study's ECG characterization and incorporated into the prespecified definition of an abnormal ECG, which included bundle-branch block (right or left), second-degree atrioventricular block, atrial fibrillation, or flutter, and a prior history of atrial fibrillation or flutter. At baseline, 21.8% of the cohort had an abnormal ECG, with right bundle-branch block present in 2.6% of patients and left bundle-branch block present in 2.2%. Second-degree atrioventricular block was uncommon but was included as a qualifying conduction abnormality that contributed to the composite ECG risk variable. Several patients had cardiac implantable electronic devices at baseline, including pacemakers and implantable cardioverter-defibrillators, primarily in carriers of high-risk genotypes such as *LMNA* or *TMEM43*; in these patients, conduction disease and family history of sudden cardiac death were contributing factors for device implantation before phenotypic DCM was present. During follow-up, ECG abnormalities, which encompassed atrioventricular conduction disease and intraventricular conduction delay via bundle-branch block, were consistently associated with incident DCM. Patients who developed DCM were more likely to have an abnormal ECG at baseline than those who did not (38.8% vs 21.0%; p < 0.001), and abnormal ECG remained an independent predictor of DCM development in multivariable Cox regression analysis (HR, 1.71; 95% CI, 1.08-2.71). Conduction disease also appeared clinically consequential in longitudinal outcomes, as several *LMNA* carriers received implantable cardioverter-defibrillators during follow-up, specifically after developing conduction disorders, prior to meeting the criteria for DCM. While the study did not report granular progression rates for individual conduction phenotypes such as isolated atrioventricular block or specific intraventricular conduction delays, the aggregation of these findings indicates that early conduction system involvement is a measurable and prognostically relevant marker in genotype-positive relatives and contributes to an increased risk of subsequent DCM onset. The findings are limited by the observational design and reliance on a composite ECG variable rather than detailed longitudinal characterization of specific conduction abnormalities.

Myers et al. (2024) conducted a systematic review and meta-analysis to estimate the prevalence of genetically associated DCM in the broader DCM population. The analysis focused on variants in the *TTN* and *MYH7* genes, which represent the most common contributors to DCM. The authors identified 57 studies that met the inclusion criteria. In global adult or predominantly adult DCM populations, the median prevalence of genetic DCM was 20.2%, with *TTN*-associated DCM accounting for 11.4% and *MYH7*-associated DCM accounting for 3.2%. The prevalence of genetic DCM in pediatric populations was similar, with a weighted mean of 21.3%. The authors noted that population-level prevalence data for genetic DCM are limited and suggested that current estimates may underestimate the genetic contribution due to incomplete screening and case identification. They concluded that further epidemiological studies, including large population-based analyses that use whole-genome sequencing to capture structural and noncoding variants, are warranted. The publication by Mazzarotto et al. (2020), previously discussed in this policy, was included in this systematic review.

The Peters et al. (2022) systematic review examined the phenotypic spectrum, functional effects, natural history, and treatment outcomes that are associated with rare variants of *SCN5A* linked to DCM. The review identified 18 variants in 173 probands from 29 families. Functional evaluation was available for 11 variants, seven of which demonstrated a consistent phenotype that was characterized predominantly by frequent multifocal narrow- and broad-complex ventricular premature beats (VPBs) in 72% of affected relatives, along with atrial arrhythmias (32%), ventricular arrhythmias (33%), DCM (56%), and sudden cardiac death (13%). The VPB-predominant phenotype was not observed in variants that are associated with increased late sodium current or reduced peak current density or mixed functional effects. DCM did not occur in the absence of arrhythmias. Notably, across 12 studies that involved 23 individuals, sodium channel–blocking therapy was reported to be effective in treating VPB-predominant cardiomyopathy. The authors concluded that *SCN5A* variants manifest with heterogeneous primary arrhythmic features, with most DCM-associated variants causing a

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multifocal, VPB-predominant cardiomyopathy that appears reversible with sodium channel blockade. They emphasized that early recognition of this distinctive phenotype and appropriate genetic testing are critical for optimal management of individuals with *SCN5A*-associated DCM.

Left Ventricular Noncompaction Cardiomyopathy

The Mester et al. (2025) single-center observational study examined blood relatives of participants with genetically determined left ventricular excessive trabeculation (LVET), framed as a morphological phenotype that may overlap with or precede left ventricular noncompaction (LVNC) cardiomyopathy. The stated objective was to evaluate the genetic, clinical, ECG, and echocardiographic involvement of relatives of probands with LVET/LVNC and pathogenic or likely pathogenic mutations. Overall, 18 probands with LVET that was confirmed by CMR imaging criteria commonly applied to LVNC diagnosis were identified, along with 55 blood relatives (children and adults; mean age, 44 ±20.8 years). The relatives underwent structured family and personal history assessment, 12-lead ECG, transthoracic echocardiography, and targeted Sanger sequencing for the index mutation. A pathogenic or likely pathogenic mutation that was associated with LVNC-overlapping cardiomyopathies was identified in 38% of relatives, and nearly 80% of families included at least one additional mutation carrier. Family histories frequently included arrhythmias, stroke, syncope, sudden cardiac death, and implanted cardiac devices, which are clinical features that are commonly reported in LVNC populations, while personal histories revealed a high prevalence of subjective symptoms and arrhythmias despite generally preserved ventricular function. When analyzed by genetic status, relatives who were carrying the index mutation did not differ from noncarriers with respect to left ventricular volumes, global systolic function, and strain parameters, and echocardiographic findings were largely within normal ranges; this suggests incomplete penetrance of LVNC morphology despite pathogenic genetics. However, most participants who fulfilled the Jenni criteria for LVET (interpreted here as an LVNC-type morphology) were mutation carriers, and these participants had a significantly lower LVEF than those without LVNC morphology, although ejection fraction typically remained in the normal range. ECG differences between genetic subgroups included lower left ventricular Sokolow-Lyon index values and shorter QT duration in mutation carriers, which are findings that the authors discussed in the context of structural remodeling and the potential ion channel involvement described in LVNC. The authors concluded that a substantial proportion of relatives of genetically affected individuals with LVET/LVNC have genetic carriage and echocardiographic morphological features that are consistent with LVNC, accompanied by subtle functional differences; this supports the relevance of family evaluation in this population. The findings are limited by the nonrandomized, observational design; modest sample size; lack of a formal control group; short-term, cross-sectional assessment; absence of CMR imaging in relatives; and restriction to a single, ethnically homogeneous population, which together limit inference about progression to overt LVNC cardiomyopathy or long-term clinical outcomes.

The Farkas-Sütő et al. (2024) retrospective, single-center, observational study examined whether genetic findings distinguish structural, ECG, and clinical features in patients with LVET and preserved LVEF. Genetic testing, using a 174-gene cardiomyopathy panel, was performed in 55 of 69 enrolled patients with LVET (29 female; mean age, 37.7 ±13.9 years), with variants classified according to ACMG criteria into benign, VUS, or pathogenic/likely pathogenic groups. Across genetic subgroups, no statistically significant differences were observed in any CMR imaging measures, including indexed left or right ventricular end-diastolic or end-systolic volumes, stroke volumes, total or trabeculated myocardial mass, or ejection fraction, indicating no genotype-associated differences in ventricular structure or global systolic function in this cohort with preserved ejection fraction. Among ECG parameters, only QTc duration differed significantly between genetic subgroups, with a significant difference reported between the VUS and pathogenic groups ($p < 0.05$), while all other ECG parameters showed no statistically significant between-group differences. When genetic subgroups were compared with their age- and sex-matched control populations, genotype-specific electrical differences emerged. In the benign variant subgroup, patients with LVET had a significantly longer P-wave duration than controls (113.8 ±7.7 ms vs 99.6 ±16.9 ms; $p < 0.01$), with no other ECG differences reaching statistical significance. In contrast, the VUS subgroup had a significantly prolonged QRS duration (105.7 ±12.3 ms vs 97.4 ±10.4 ms; $p = 0.01$) and QT interval (393.4 ±33.5 ms vs 375.3 ±21.8 ms; $p = 0.023$), lower P-wave amplitude (0.10 ±0.04 mV vs 0.13 ±0.04 mV; $p = 0.009$), lower T-wave amplitude (0.16 ±0.16 mV vs 0.26 ±0.09 mV; $p = 0.014$), and higher right ventricular Sokolow-Lyon index (7.6 ±4.5 mm vs 5.3 ±2.3 mm; $p = 0.047$) compared with controls. The pathogenic variant subgroup had a significantly longer P-wave duration (109.5 ±16.0 ms vs 99.1 ±10.3 ms; $p = 0.043$), longer QT interval (405.6 ±31.0 ms vs 374.8 ±35.7 ms; $p = 0.018$), longer QTc (435.5 ±24.7 ms vs 406.3 ±26.8 ms; $p = 0.04$), and lower T-wave amplitude (0.17 ±0.13 mV vs 0.27 ±0.07 mV; $p = 0.019$) than controls. Correlation analyses further showed that associations between QRS duration and right ventricular Sokolow-Lyon index with ventricular volumes and myocardial mass were stronger when analyses were restricted to pathogenic variant carriers. The authors concluded that while genetic status did not differentiate patients with LVET by structural phenotype, the presence of VUSs or pathogenic variants was associated with statistically significant ECG abnormalities and a higher prevalence of arrhythmic events and positive family history. The applicability of these findings is limited by the small subgroup sample sizes and retrospective design.

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The Grebur et al. (2024) cross-sectional observational study aimed to characterize the genetic background, CMR imaging features, and clinical manifestations in symptomatic participants with an LVNC phenotype and preserved LVEF and to examine genotype-phenotype relationships. The investigators enrolled 54 symptomatic participants who had isolated LVNC and preserved LVEF (≥ 50%) and 54 age- and sex-matched healthy controls, all from a Caucasian population; participants were recruited at a single CMR imaging center. LVNC was defined using Petersen and Jacquier CMR imaging criteria; participants with a reduced LVEF, overlapping cardiomyopathies, hypertension, significant comorbidities, or potential causes of transient hypertrabeculation were excluded. The LVNC group had a mean age of 39 ±14 years and a mean LVEF of 65% ±5%. CMR imaging analyses included ventricular volumes, mass, trabeculated and papillary muscle mass, ejection fraction, and feature tracking–derived global longitudinal and circumferential strain. Clinical data were obtained from questionnaires and medical records, and predefined clinical risk factors and adverse features were categorized as red flags. All participants with LVNC underwent cardiogenetic counseling and next-generation sequencing with a 174-gene cardiomyopathy panel, with variants classified according to ACMG criteria. While their functional CMR imaging parameters were largely within reference ranges, participants with LVNC individuals had significantly higher indexed left ventricular volumes and myocardial mass and a significantly lower LVEF, global longitudinal strain, and global circumferential strain than controls. Pathogenic or likely pathogenic cardiomyopathy-associated variants were identified in 24% of participants with LVNC, VUSs were identified in 56%, and no relevant mutations were identified in 20%. The most frequently affected genes among pathogenic variants were *TTN*, *MYH7*, and *TNNT2*, and all detected variants were heterozygous. CMR imaging functional and strain parameters did not differ significantly among genetic subgroups and did not correlate with genotype. In contrast, clinical features differed by genetic classification. A higher prevalence of positive family history of cardiomyopathy or sudden cardiac death and thromboembolic events was observed in participants with pathogenic or uncertain variants, and sudden cardiac death and increased left ventricular end-diastolic volume index occurred only in those with pathogenic variants. The presence and number of red flags per participant differed significantly across genetic subgroups and were moderately correlated with genotype, with participants who carried pathogenic variants, particularly those with mutations that were directly associated with LVNC, having the highest red flag burden. Most participants who were diagnosed in childhood were found to have pathogenic or uncertain variants. The authors concluded that genetic involvement is common in symptomatic LVNC with preserved LVEF and that clinical risk features cluster more frequently in genetically affected individuals despite similar imaging phenotypes. The study's findings are limited by the study's cross-sectional design, lack of longitudinal outcomes, and modest subgroup sizes, which restrict conclusions regarding prognosis and long-term clinical impact.

The de Uña-Iglesias et al. (2024) multicenter observational study assessed the diagnostic contribution of systematic copy number variant (CNV) analysis in hereditary cardiomyopathies, including LVNC, using next-generation sequencing. The study population comprised 11,647 unrelated participants of predominantly western Caucasian heritage who were referred by clinical specialists for confirmed or suspected cardiomyopathy. All underwent sequencing and CNV detection using a 170-gene panel, with findings classified according to ACMG criteria. Among the cohort, 668 participants were indicated by clinicians as having LVNC, with allowance for overlapping phenotypes. In this LVNC subgroup, 12 pathogenic or likely pathogenic CNVs were identified, which resulted in a diagnostic yield of 1.8% (12 of 668 participants) across all tested cases and 5.8% among genetically positive LVNC studies. These CNVs were distributed across multiple genes rather than concentrated at a single locus, most frequently involving *DMD*, *TTN*, *RYR2*, and *PRDM16*, and consisted primarily of deletions; most were heterozygous, with hemizygous events observed in X-linked *DMD* cases. The authors contrasted these findings with those of prior studies in LVNC, which reported yields below 1% or detected no pathogenic CNVs, attributing the higher yield in the present study to the larger sample size and broader gene coverage. The authors concluded that systematic CNV analysis modestly, but meaningfully, increases diagnostic yield in LVNC; they also noted that the study's noncomparative design, reliance on clinician-reported phenotypes, limited population diversity, absence of longitudinal follow-up, and lack of assessment of downstream clinical impact constrain interpretation and that well-designed, comparative studies are needed.

The van Waning et al. (2019) systematic review evaluated genotype-phenotype correlations in LVNC cardiomyopathy from 172 published studies. The researchers compared age at diagnosis, cardiac characteristics, and risk for major adverse cardiac events in relation to mode of inheritance and molecular effects for defects in common sarcomere genes and LVNC subtypes in 561 individuals (244 children, 297 adults, and 20 individuals with no recorded age at presentation, who were excluded from age-based quantitative analysis). The main findings in adults were single missense mutations in sarcomere genes, whereas children more frequently had X-linked or mitochondrial defects ($p = 0.001$) or chromosomal abnormalities ($p < 0.001$). Children had an increased risk of congenital heart defects ($p < 0.001$) and major adverse cardiac events ($p < 0.001$). *MYH7* was implicated in 48% of the sarcomere gene variations. Mutations in *MYH7* and *ACTC1* were associated with a lower risk for major adverse cardiac events than mutations in *MYBPC3* and *TTN* ($p = 0.001$). The LVNC/DCM phenotype was the most common subtype (56%; $p = 0.022$) and was associated with an elevated risk for major adverse cardiac events as well as a high risk for left ventricular systolic dysfunction ($p < 0.001$). Genetic predictors for major adverse cardiac events were variants in *MYBPC3* or *TTN*; arrhythmia; nonsarcomere, nonarrhythmia cardiomyopathy; and X-linked gene variants. The study was limited by the inclusion of mostly case reports or small case

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series, and the study design did not allow identification of the differences in prognosis between identified genetic and other causes of LVNC. Based on this study's results, the authors proposed that clinical and diagnostic management of individuals with LVNC should be modified according to age at presentation and that identifying the genetic cause of LVNC could aid in the clinical management of affected individuals and their families. The publication by van Waning et al. (2018), previously discussed in this policy, was included in this systematic review.

Clinical Practice Guidelines

American College of Cardiology (ACC)/American Heart Association (AHA)

In Ommen et al. (2024), the AHA and ACC, in collaboration with the American Medical Society for Sports Medicine, HRS, Pediatric and Congenital Electrophysiology Society, and Society for Cardiovascular Magnetic Resonance, published updated guidelines on the management of HCM. These recommendations were developed following a comprehensive evaluation of applicable literature that was published through May 23, 2023, by the writing committee. Regarding genetic testing of affected patients and screening of family members, the guidelines include the following recommendations:

- Evaluation of familial inheritance, including a three-generation family history, is recommended for patients with HCM as part of the initial assessment (class of recommendation: 1/strong; level of evidence: B-NR). (Moderate-quality evidence from one or more well-executed studies, including nonrandomized, observational, or registry as well as meta-analyses of such studies.)
- Genetic testing in patients with HCM is helpful to determine whether there is a genetic basis for disease and thereby can aid in the identification of family members who may be at risk for developing HCM (cascade testing; class of recommendation: 1/strong; level of evidence: B-NR).
- When HCM presents atypically or when another genetic condition is suspected, workup that includes genetic testing for HCM, along with other causes of unexplained cardiac hypertrophy, is recommended (class of recommendation: 1/strong; level of evidence: B-NR).
- Genetic counseling by qualified experts is recommended for all patients with HCM to discuss risks, benefits, test results, and the clinical significance of those results in a shared decision-making process (class of recommendation: 1/strong; level of evidence: B-NR).
- When genetic testing is performed in a proband with HCM, the initial genes being tested should include those with strong evidence associated with HCM disease (at the time of publication, these include *MYH7, MYBPC3, TNNI3, TNNT2, TPM1, MYL2, MYL3*, and *ACTC1*; class of recommendation: 1/strong; level of evidence: B-NR).
- Both clinical screening as well as cascade testing should be offered to relatives of patients with HCM when a pathogenic/likely pathogenic variant has been identified in the proband (class of recommendation: 1/strong; level of evidence: B-NR).
- When sudden, unexplained death has occurred, with a postmortem diagnosis of HCM, postmortem genetic testing is helpful to assist with cascade testing as well as clinical screening in first-degree relatives (class of recommendation: 1/strong; level of evidence: B-NR).
- In patients with HCM who have undergone genetic testing, serial testing of the clinical significance of the variants is recommended to evaluate for variant reclassification that could impact diagnosis and familial cascade testing (class of recommendation: 1/strong; level of evidence: B-NR).
- Preconception and prenatal reproductive and genetic counseling should be offered in families that are affected by HCM (class of recommendation: 1/strong; level of evidence: B-NR).
- The utility of genetic testing for the purpose of assessing the risk of sudden cardiac death in patients with HCM is uncertain (class of recommendation: 2b/weak; level of evidence: B-NR).
- The utility of genetic testing for the purposes of variant reclassification performed on phenotype-negative family members of patients with HCM who were found to have only a VUS is uncertain (class of recommendation: 2b/weak; level of evidence: B-NR).
- In patients with HCM for whom genetic testing revealed no pathogenic variants, cascade testing of relatives is not useful (class of recommendation: 3/no benefit; level of evidence: B-NR).
- Ongoing clinical screening in genotype-negative relatives, when genotype-positive HCM has been identified in the family, is not indicated unless the variant has been downgraded to a VUS, likely benign variant, or benign variant.

American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA)

In 2022, the AHA/ACC/HFSA (Heidenreich et al.) published updated heart failure guidelines, which advise that genetic screening and counseling are recommended to detect cardiac disease and to prompt consideration of treatments, with the aim of decreasing heart failure progression and sudden death in first-degree relatives of select patients with genetic or inherited cardiomyopathies (class of recommendation: 1; level of evidence: B-NR). The guidelines also note that in select patients with nonischemic cardiomyopathy, referral for genetic counseling and testing is reasonable to identify conditions that could guide treatment for patients and family members (class of recommendation: 2a; level of evidence: B-NR).

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American Heart Association (AHA)

The AHA (Landstrom et al.) published a scientific statement in 2021 that addresses the use of genetic testing for heritable cardiovascular conditions, such as cardiac channelopathies, cardiomyopathies, and aortopathies, in pediatric populations. The statement notes that genetic testing can be considered for children with suspected or increased risk of cardiovascular disease, emphasizing the need for multidisciplinary counseling and careful consideration of test timing. These decisions should be individualized based on the patient, family context, and suspected condition. The authors also highlight the importance of longitudinal follow-up to reassess variant pathogenicity and to address the evolving clinical and psychosocial needs of affected patients and their families.

European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS)

In an expert consensus statement on genetic testing for cardiac disease, the EHRA, HRS, APHRS, and LAHRS (Wilde et al., 2022) provide the following recommendations for genetic testing in cardiomyopathies.

Hypertrophic Cardiomyopathy

- For genetic testing in a proband with HCM (including those cases diagnosed post mortem), the initial tier of genes that are tested should include genes with definitive or strong evidence of pathogenicity (currently *MYH7, MYBPC3, TNNI3, TPM1, MYL2, MYL3, ACTC1,* and *TNNT2*). (Supported by strong observational evidence and authors' consensus.)
- For genetic testing in a proband with HCM, the initial tier of genes that are tested may include genes with moderate evidence of pathogenicity (*CSRP3, TNNC1,* and *JPH2*). (Some evidence and general agreement favor usefulness/efficacy of a test.)
- In patients with HCM, genetic testing is recommended for identification of family members who are at risk of developing HCM. (Supported by strong observational evidence and authors' consensus.)
- In patients with an atypical clinical presentation of HCM or when another genetic condition that is associated with unexplained hypertrophy is suspected (e.g., HCM phenocopy), genetic testing is recommended. (Supported by strong observational evidence and authors' consensus.)
- Predictive genetic testing in related children is recommended in those who are aged > 10 to 12 years. (Supported by strong observational evidence and authors' consensus.)
- In patients with HCM who harbor a VUS, the usefulness of genetic testing in phenotype-negative relatives for the purpose of variant reclassification is uncertain. (Some evidence and general agreement favor usefulness/efficacy of a test.)
- Predictive genetic testing in related children who are aged below 10 to 12 years may be considered, especially when there is a family history of early-onset disease. (Some evidence and general agreement favor usefulness/efficacy of a test.)
- In patients with HCM who harbor a VUS, testing of affected family members for the purpose of variant classification may be considered. (Supported by strong observational evidence and authors' consensus.)
- In patients with HCM in whom genetic testing found no pathogenic/likely pathogenic variants, cascade genetic testing of family relatives is not recommended. (There is evidence or general agreement not to recommend a test.)
- Ongoing clinical screening is not recommended in genotype-negative relatives in most families with genotype-positive HCM. (There is evidence or general agreement not to recommend a test.)

Arrhythmogenic Cardiomyopathy

- Comprehensive genetic testing is recommended for all patients with consistent phenotypic features of ACM, including those cases diagnosed post mortem, whatever familial context. (Supported by strong observational evidence and authors' consensus.)
- Genetic testing of first-tier definitive disease-associated genes (currently *PKP2, DSP, DSG2, DSC2, JUP, TMEM43, PLN*, *FLNC, DES,* and *LMNA*) is recommended. (Supported by strong observational evidence and authors' consensus.)
- Owing to the possibility of complex genotypes, in families with multiple affected members, the case with the more severe and/or earlier phenotype may be considered the genetic proband and be tested first. (Some evidence and general agreement favor usefulness/efficacy of a test.)
- In patients with a borderline ACM phenotype, comprehensive genetic testing may be considered. The identification of a pathogenic/likely pathogenic genetic variant would be useful to confirm the diagnosis. (Some evidence and general agreement favor usefulness/efficacy of a test.)
- Variant-specific genetic testing is recommended for family members and appropriate relatives following the identification of the disease-causative variant. (Supported by strong observational evidence and authors' consensus.)

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- Predictive genetic testing in related children is recommended in those who are aged > 10 to 12 years. (Supported by strong observational evidence and authors' consensus.)
- Predictive genetic testing in related children who are aged below 10 to 12 years may be considered, especially when there is a family history of early-onset disease. (Some evidence and general agreement favor usefulness/efficacy of a test.)

Dilated Cardiomyopathy

- Genetic testing is recommended for probands with DCM and a family history of DCM, and the initial tier of genes that are tested should include genes with definitive or strong evidence of pathogenicity (currently *BAG3, DES, FLNC, LMNA, MYH7, PLN, RBM20, SCN5A, TNNC1, TNNT2, TTN,* and *DSP*). (Supported by strong observational evidence and authors' consensus.)
- For genetic testing in a proband with DCM, the initial tier of genes that are tested may include genes with moderate evidence of pathogenicity (*ACTC1, ACTN2, JPH2, NEXN, TNNI3, TPM1,* and *VCL*). (Some evidence and general agreement favor usefulness/efficacy of a test.)
- Genetic testing is recommended for patients with DCM and a family history of premature, unexpected, sudden death or in a patient with DCM who has clinical features that are suggestive of a particular/rare genetic disease (such as atrioventricular block or sinus dysfunction or creatine phosphokinase elevation). (Supported by strong observational evidence and authors' consensus.)
- Genetic testing can be useful in patients with apparently sporadic DCM, particularly in the presence of either severe systolic dysfunction (LVEF < 35%) or a malignant arrhythmia phenotype (e.g., sustained ventricular tachycardia/fibrillation) or at a younger age. (Some evidence and general agreement favor usefulness/efficacy of a test.)
- Genetic testing may be considered for patients with DCM that is related to an acquired or environmental cause that may overlap with a genetic cause (such as peripartum or alcoholic cardiomyopathy). (Some evidence and general agreement favor usefulness/efficacy of a test.)
- Genetic testing is useful in patients with DCM to improve risk stratification and guide therapy. (Some evidence and general agreement favor usefulness/efficacy of a test.)
- Variant-specific genetic testing is recommended for family members and appropriate relatives following the identification of the disease-causative variant. (Supported by strong observational evidence and authors' consensus.)
- Predictive genetic testing in related children is recommended in those who are aged > 10 to 12 years. (Supported by strong observational evidence and authors' consensus.)
- Predictive genetic testing in related children who are aged below 10 to 12 years may be considered, especially when there is a family history of early-onset disease. (Some evidence and general agreement favor usefulness/efficacy of a test.)

Left Ventricular Noncompaction Cardiomyopathy

- LVNC cardiomyopathy genetic testing may be useful in patients in whom a cardiologist has established a clinical diagnosis of LVNC, based on examination of the patient's clinical history, family history, and ECG/echocardiographic/magnetic resonance imaging phenotype. (Some evidence and general agreement favor usefulness/efficacy of a test.)
- Genetic testing may be useful in patients with a clinical diagnosis of LVNC cardiomyopathy that is associated with other cardiac or noncardiac syndromic features. (Some evidence and general agreement favor usefulness/efficacy of a test.)
- Genetic testing should not be performed in isolated (incidental) LVNC with normal left ventricular function, no associated syndromic features, and no family history. (There is evidence or general agreement not to recommend a test.)
- Variant-specific genetic testing may be considered in family members and appropriate relatives following the identification of the disease-causative variant. (Some evidence and general agreement favor usefulness/efficacy of a test.)

Unexplained Cardiac Arrest

- In survivors of unexplained cardiac arrest, genetic testing of cardiomyopathy genes may be considered. (Some evidence and general agreement favor usefulness/efficacy of a test.)
- In relatives of survivors of unexplained cardiac arrest or relatives of those who have experienced sudden cardiac death, in whom a pathogenic variant has been identified, predictive genetic testing should be performed. (Supported by strong observational evidence and authors' consensus.)
- In survivors with cardiac arrest in whom a nongenetic cause has been identified, genetic testing of the index case should not be performed. (There is evidence or general agreement not to recommend a test.)

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Heart Failure Society of America (HFSA)/American College of Medical Genetics and Genomics (ACMG)

In 2018, the HFSA updated their guideline that addresses the genetic evaluation of cardiomyopathy in collaboration with the ACMG (Hershberger et al., 2018). This document, written by cardiologists and genetics professionals with expertise in both adult and pediatric cardiomyopathy, provides the following directives:

- Obtaining a family history of at least three generations, including the creation of a pedigree, is recommended for all patients with a primary cardiomyopathy.
- Clinical (phenotypic) screening for cardiomyopathy in at-risk first-degree relatives is recommended.
- Referral of patients with genetic, familial, or other unexplained forms of cardiomyopathy to expert centers is recommended.
- Genetic testing is recommended for patients with cardiomyopathy.
- Genetic testing is recommended for the most clearly affected family member.
- Cascade genetic testing of at-risk family members is recommended for pathogenic/likely pathogenic variants.
- In addition to routine newborn screening tests, specialized evaluation of infants with cardiomyopathy is recommended, and genetic testing should be considered.
- Genetic counseling is recommended for all patients with cardiomyopathy and their family members (level of evidence: A).
- Focused cardiovascular phenotyping is recommended when pathogenic/likely pathogenic variants in cardiomyopathy genes, designated for the reporting of secondary findings by the ACMG, are identified in a patient.
    - If a cardiovascular phenotype is identified, as would be predicted by currently available knowledge of the gene/variant pair, all usual approaches that are described elsewhere in the HFSA guidelines for a genetic evaluation, including family-based approaches, are recommended.
    - If no cardiovascular disease phenotype is identified in the patient, recommendations for surveillance screening at intervals should be considered.
    - If no cardiovascular phenotype is identified in the patient, cascade evaluation of at-risk relatives may be considered, tempered by the strength of evidence supporting the pathogenicity of the variant, the usual age at onset of the gene/variant pair, and pedigree information (e.g., ages of at-risk family members, other previously known cardiovascular clinical data in the pedigree, related information).
- Medical therapy based on cardiac phenotype is recommended, as outlined in consensus guidelines (level of evidence: A).
- Device therapies for arrhythmia and conduction system disease, based on cardiac phenotype, are recommended, as outlined in consensus guidelines (level of evidence: B).
- In patients with cardiomyopathy and significant arrhythmia or a known risk of arrhythmia, an implantable cardioverter-defibrillator may be considered before the LVEF falls below 35% (level of evidence: C).

Levels of evidence

- A: Genetic evaluation or testing has a high correlation with the cardiomyopathic disease of interest in studies with a moderate or large sample size.
- B: Genetic evaluation or testing has a high correlation with the cardiomyopathic disease of interest in smaller or single-center studies.
- C: Genetic evaluation or testing correlates with the cardiomyopathic disease of interest in case reports.

Heart Rhythm Society (HRS)

In 2019, Towbin et al. published an HRS expert consensus statement on the evaluation, risk stratification, and management of ACM and LVNC cardiomyopathy, which includes the following:

Arrhythmogenic Cardiomyopathy

- In individuals with a clinical diagnosis of ACM, genetic testing of the established ACM susceptibility genes is recommended (class of recommendation: 1; level of evidence: C-EO).
- For genetic testing of the established ACM susceptibility genes, comprehensive analysis of all established genes with full coverage is recommended (class of recommendation: 1; level of evidence: C-EO).
- The interpretation of a cardiac genetic test by a team of providers with expertise in genetics and cardiology can be useful (class of recommendation: 2a; level of evidence: C-EO).

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Left Ventricular Noncompaction Cardiomyopathy

- If the proband has a disease-causing gene variant, it is recommended that first-degree relatives of patients with LVNC undergo clinical screening for the disease, along with genetic counseling and genetic testing (class of recommendation: 1; level of evidence: B-NR).
- In patients with a clinical diagnosis of pathological LVNC, genetic counseling and genetic testing are reasonable for diagnosis and for gene-specific targeted cascade family screening (class of recommendation: 2a; level of evidence: B-NR).

Thoracic Aortic Disease

The Erez et al. (2025) retrospective, single-center, observational study evaluated the clinical effectiveness of the 2022 ACC/AHA genetic testing guidelines on thoracic aortic aneurysm by analyzing thoracic aortic disease (TAD) panel testing that was performed between August 2012 and September 2023. The study included 1,034 patients who were aged 18 years or older, had a thoracic aortic diameter of > 4 cm, and underwent multigene panel testing; those who lacked verifiable family history documentation were excluded. The cohort had a median age of 61.9 years and was predominantly White (86.8%). Patients were categorized according to guideline-specified criteria that were present at the time of testing referral: age < 60 years; syndromic features of connective tissue disease; family history of TAD, peripheral/intracranial aneurysm, or sudden unexpected death at a relatively young age in a first- or second-degree relative; or no criteria met. Patients were allowed to contribute to multiple groups. Genetic testing was conducted at a single academic laboratory or a commercial laboratory using high-throughput sequencing, and variants were classified according to ACMG standards as pathogenic, VUS, or negative. Genes were prespecified as primary if they were strongly associated with heritable TAD or secondary if they were weakly or moderately associated. Overall, 3.97% of patients had pathogenic variants, and 27.27% had VUSs. Pathogenic mutation rates differed by testing criterion. Pathogenic mutations occurred most frequently in patients with syndromic connective tissue disease features (13.2%), followed by those who were younger than 60 years (5.48%), those with a family history (4.63%), and those who met no criteria (2.21%), with statistically significant differences across groups. When analysis was limited to primary genes, the overall pathogenic rate was 3.29%, and the VUS rate was 12.19%; secondary genes yielded a pathogenic rate of 0.68% and a higher VUS rate of 17.5%. Combinations of criteria substantially influenced pathogenic yield, with patients who met all three criteria having a pathogenic mutation rate of 22%; the rates were 0.54% in patients who were younger than 60 years alone and 0.63% in those who met no criteria. The authors concluded that the diagnostic yield of genetic testing under current guidelines varies widely by individual and that incorporating multiple criteria improves risk stratification compared with applying criteria independently. Testing genes without definitive associations with heritable TAD produced few pathogenic findings and a high prevalence of VUSs, which limits clinical utility. The study is limited by its retrospective design, reliance on medical record documentation to determine eligibility criteria, evolving gene panels and variant classification during the study period, and single-center setting, which may restrict generalizability. The cohort was predominantly White, and the authors noted that disparities related to insurance coverage, socioeconomic status, and access to testing may have influenced which patients underwent genetic evaluation. The findings suggest that refining testing guidelines to emphasize combined criteria and primary genes may improve genetic risk stratification while reducing inconclusive results and that well-designed, comparative and prospective studies are needed.

The DePaolo et al. (2025) observational genetic association and predictive modeling study aimed to determine whether common genetic variation, independent of aortic diameter, can improve identification of individuals who are at risk for thoracic aortic dissection. The investigators used summary statistics from multipopulation genome-wide association studies to identify 43 significant loci from which a PRS was constructed. The score was applied to 43,249 participants in the biobank of a single health system with linked electronic health records. Thoracic aortic dissection was identified using diagnostic codes, and analyses were adjusted for age, sex, clinical risk factors, and measured ascending aortic diameter, when available. In the biobank, 261 participants had prevalent dissection, and 159 experienced incident dissection during a median follow-up of approximately 9 years. Participants with dissection were older, more often male, and had higher prevalence of hypertension and pathogenic or likely pathogenic hereditary thoracic aortic aneurysm and dissection gene variants. The PRS showed a strong association with prevalent dissection, with an odds ratio of 2.13 per 1-SD increase, which remained statistically significant after adjustment for clinical risk factors and ascending aortic diameter; however, it was attenuated. Incorporation of the PRS into predictive models modestly improved calibration and discrimination compared with models that included age, sex, clinical risk factors, and aortic diameter alone, increasing the area under the receiver operating characteristic curve from 0.676 to 0.723. The authors concluded that a common-variant PRS can predict thoracic aortic dissection, independent of aortic diameter, and improves predictive model performance in diverse biobank populations. This study's findings were limited by the observational design, reliance on diagnostic codes for outcome ascertainment, enrichment of dissection cases in the primary cohort, rarity of the outcome, lack of prospective testing, potential population structure effects in the genetic modeling, and limited power in ancestry-stratified analyses. Well-designed, prospective studies are needed to evaluate the clinical utility of incorporating the PRS into dissection risk stratification and management decisions.

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The DePaolo et al. (2024) study evaluated whether the incorporation of a polygenic score improves the prediction of ascending thoracic aortic dilation beyond an established clinical risk model in a diverse population. The investigators conducted an observational modeling study that included 6,235 adult individuals from an institutional biobank who had available transthoracic echocardiography, clinical data, and genome-wide genotype data. Individuals with prior thoracic aortic surgery or dissection and those not genetically similar to African or European reference populations were excluded. The cohort had a median age of 61 years, 55% were male, and 33% were genetically similar to an African reference population. The mean ascending aortic diameter was 3.36 cm, and 11.7% of individuals met the ≥ 4.0-cm threshold. The objective was to assess whether adding a national biobank–derived polygenic score for ascending aortic diameter to the previously published AORTA (Aorta Optimized Regression for Thoracic Aneurysm) score improves model performance. Compared with the AORTA score alone, the addition of the national biobank–derived polygenic score increased the proportion of variance explained in ascending aortic diameter from 30.6% to 33.1%, with further improvement to 34.9% after model reweighting. These improvements were consistently observed among individuals who were genetically similar to a European reference population but were minimal among those who were genetically similar to an African reference population. Comparable ancestry-dependent patterns were observed for discrimination of dilation of ≥ 4.0 cm and for decision curve analyses that assessed clinical net benefit. The authors concluded that incorporating a polygenic score that is derived from a predominantly European genome-wide association study meaningfully improves prediction of ascending thoracic aortic dilation only among individuals who are genetically similar to European reference populations and offers little additional value in African reference populations. Limitations of this study include enrichment of the biobank for cardiovascular disease, single-center design, potential variability in echocardiographic measurements across readers, derivation of both the clinical score and the polygenic score from a less diverse population, and uncertainty regarding generalizability to other cohorts. The findings suggest that current integration of this polygenic score may exacerbate health care disparities and that the standard AORTA score remains the most unbiased screening approach in diverse clinical populations until more representative genomic data are available.

The Ghazy et al. (2024) retrospective, single-center, observational cohort study evaluated the prevalence and clinical impact of genetic variants in patients who survived surgical or endovascular treatment for thoracic aortic aneurysm or dissection. Patients who were aged 18 to 80 years and underwent repair between 2008 and 2019 were eligible, with exclusions for inflammatory or traumatic etiology, missed follow-up, and age over 60 years without offspring. Of 1,334 screened cases, 95 patients who had complete clinical, imaging, and genetic data were enrolled. The cohort was predominantly male (71%), with a mean age at diagnosis of approximately 52 years, and most patients underwent open surgery (68%) rather than thoracic endovascular repair. Follow-up imaging with computed tomography angiography at 3 months, 9 months, and annually thereafter, supplemented by magnetic resonance imaging or echocardiography when appropriate, was conducted for a mean of 3.0 ±2.5 years. Genetic testing was performed using next-generation sequencing of an initial nine-gene panel that was associated with TAD, expanded up to 32 genes in cases of specific suspicion. Genetic variants in aortic disease–associated genes were identified in 40.7% of patients, with the majority being classified as VUSs and 7.4% harboring a pathogenic variant, most commonly involving *FBN1*. When analyzed by primary diagnosis, genetic variants were not associated with persistence of pathology, aneurysm growth, development of new aneurysms, or reintervention rates in patients who were initially treated for aneurysm, and no overall association with reintervention was observed. Among patients who were treated for aortic dissection, variant class was associated with persistence of dissection ($p = 0.037$) but not with progression or reintervention when analyzed in isolation. In contrast, when all patients with a detected dissection on follow-up imaging were considered together, regardless of original pathology, the presence of genetic variants correlated with disease progression ($p = 0.012$) and higher reintervention rates ($p = 0.047$). The authors concluded that genetic variants, including VUSs, are common in individuals with TAD and may be associated with worse follow-up outcomes in those with persistent or new dissection; this supports broader genetic testing in this subgroup. The findings are limited by the retrospective, single-center design; lack of a comparison group; absence of masking or randomization; small sample size; modest follow-up duration for a chronic condition; and limited power for subgroup analyses, all of which constrain the strength and generalizability of the conclusions.

The Abood et al. (2024) single-center, retrospective, observational study examined whether genetic variant classification is associated with disease severity and progression in adults with thoracic aortic aneurysm and dissection involving the aortic root and/or ascending aorta. Consecutive, unoperated patients who were evaluated at a specialty clinic between 2011 and 2020 were included, with inclusion based on prespecified echocardiographic criteria for thoracic aortic enlargement. Overall, 407 patients were included, with a mean age of 53.7 years; 64.4% were male, 88.9% were White, and 38% reported a family history of thoracic aortic aneurysm or dissection. Comprehensive aortopathy genetic testing was performed using commercial panels that were updated over time, and variants were classified according to ACMG criteria into pathogenic/likely pathogenic variants, VUSs, or gene-negative findings. Demographic, clinical, and serial echocardiographic data and family history were abstracted from medical records. Pathogenic/likely pathogenic variants were found in 37 patients (9.1%), 147 patients (36.1%) had a VUS, and 223 (54.7%) were gene negative. The primary analyses compared maximal aortic aneurysm diameter and aneurysm growth rates across genetic groups using multivariable linear regression and mixed-effects modeling, adjusting for relevant demographic and clinical factors.

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Patients with pathogenic/likely pathogenic variants had significantly larger maximal aortic diameters than those with VUSs or gene-negative findings, with an adjusted mean increase of 4.78 mm associated with pathogenic/likely pathogenic status ($p < 0.001$). Among 162 patients who had serial echocardiographic follow-up, aneurysm growth rates were significantly higher in the pathogenic/likely pathogenic group at 1.36 mm per year (95% CI, 0.77-1.95 mm) compared with 0.83 mm per year in the VUS group (95% CI, 0.66-0.99 mm) and 0.89 mm per year in the gene-negative group (95% CI, 0.79-0.99 mm; $p < 0.001$). Each additional millimeter of aneurysm diameter was associated with a 20% higher likelihood of eventual surgical intervention. While average growth rates for aneurysms associated with VUSs were similar to those in gene-negative patients, marked heterogeneity in individual growth trajectories was observed. The authors concluded that pathogenic/likely pathogenic variants are associated with faster aneurysm progression and larger aneurysm size, supporting closer surveillance and earlier intervention in this group while emphasizing cautious individualized follow-up and familial genetic evaluation in those with VUSs. The findings are limited by the retrospective, single-center design; predominantly White population; and limited follow-up duration for a slow-progressing disease, all of which constrain generalizability and confidence in long-term outcome interpretation.

The Mahlmann et al. (2024) single-center observational study evaluated whether histological examination of the resected aortic wall can predict the presence of genetic thoracic proximal aortopathies in individuals who are undergoing surgery for thoracic aortic aneurysm or dissection. The authors analyzed 65 participants who underwent open surgical treatment between 2011 and 2021 and subsequently completed both histopathologic assessment of aortic specimens and next-generation sequencing–based genetic testing. The cohort had a mean age of 48.4 years and was predominantly male, with all aneurysms and dissections involving the proximal thoracic aorta. Eligible participants underwent surgery before age 60 years or up to age 80 years if they had offspring, and cases with traumatic, inflammatory, or iatrogenic etiologies were excluded. Histological evaluation followed established Society for Cardiovascular Pathology criteria and included assessment of media degeneration, elastic fiber abnormalities, extracellular matrix changes, smooth muscle cell and collagen alterations, and a summary judgment of whether findings suggested a connective tissue disorder. Genetic testing screened a broad panel of genes that are associated with syndromic and nonsyndromic TAD, and variants were classified according to standard pathogenicity criteria. Nearly half of the cohort had a detected genetic mutation or variant, most commonly involving *FBN1* or *MYH11*, while histological features that were suggestive of connective tissue disease were identified in approximately two-thirds of participants. The study failed to demonstrate a reliable correlation between histological findings and genetic test results, as histological signs indicative of connective tissue disease were not predictive of mutation detection by next-generation sequencing. Although participants with both histological features and confirmed genetic variants were significantly younger than those with neither, histology alone did not discriminate between participants with or without pathogenic or likely pathogenic variants. Cardiovascular risk factor burden was higher with increasing age and did not materially differ by genetic status. The authors concluded that histological examination of aortic specimens has limited diagnostic value for predicting underlying genetic aortopathy and that genetic testing is necessary for definitive characterization, particularly when histological findings are nonspecific. The study is limited by its modest sample size, lack of randomization or comparison group, heterogeneity in histological interpretation across pathologists, and inclusion of both aneurysm and dissection cases with differing pathophysiology, all of which constrain the strength and generalizability of the conclusions; well-designed, comparative studies that include larger cohorts are needed.

The Pirruccello et al. (2024) study developed and evaluated a multivariable prediction model that integrated clinical factors with a polygenic score for ascending aortic diameter to improve estimation of ascending aortic size and stratification of risk for adverse thoracic aortic events. Model development and internal validation were conducted in a national biobank, using magnetic resonance imaging–derived aortic measurements, with external validation in cohorts from a large, single-institution biobank; the All of Us biobank, using transthoracic echocardiography; and the Framingham Heart Study, using noncontrast computed tomography. Ascending aortic diameter was the primary imaging outcome, with secondary outcomes that included identification of a diameter of ≥ 4.0 cm and electronic health record–defined thoracic aortic dissection, aneurysm, and related adverse events. The polygenic score was derived from a genome-wide association study of 39,524 national biobank participants and incorporated into a clinical model that included age, sex, body size, blood pressure, heart rate, and vascular risk factors. In internal and external validation cohorts, the polygenic score explained 34.9% to 41.8% of the variance in ascending aortic diameter compared with 28.9% to 33.0% for the clinical model alone. Discrimination for identifying a diameter of ≥ 4 cm was consistently higher with the polygenic score, with area under the receiver operating characteristic curves ranging from 0.808 to 0.856 across cohorts and statistically exceeding those of the clinical model. In analyses of 401,453 national biobank participants and 164,789 All of Us participants without imaging, the polygenic score was associated with a higher risk of adverse thoracic aortic events and thoracic aortic aneurysm diagnoses than the clinical model, with HRs per SD of 2.46 and 1.58, respectively, for adverse events in the national biobank and All of Us biobank. Subgroup analyses suggested similar calibration and performance among Black or African American participants in the single-institution cohort and across ancestry groups in the All of Us biobank, although event counts were limited in several subgroups. The authors concluded that incorporating polygenic information into a clinical risk model improves estimation of ascending aortic diameter, identification of thoracic aortic dilation, and prediction of adverse thoracic aortic outcomes, including dissection. The findings are limited by the

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observational design, lack of randomization and masking, predominance of participants with European genetic backgrounds in imaging cohorts, and modest numbers of adverse events, which together limit generalizability and the strength of causal inference. Prospective and more diverse validation studies are needed.

The Gomez-Mayorga et al. (2024) retrospective cohort study analyzed thoracic endovascular aortic repair (TEVAR) outcomes in patients with genetic aortopathies using the Society for Vascular Surgery Vascular Quality Initiative registry, drawing on prospectively collected data from 2010 through 2023 across 210 centers. Adults who were undergoing TEVAR were categorized by the presence or absence of a documented genetic aortopathy, which was defined as Marfan syndrome, Loeys-Dietz syndrome, or vascular Ehlers-Danlos syndrome. Of 19,340 included patients, 304 (1.6%) had a genetic aortopathy, which was most commonly Marfan syndrome (87%). Patients with a genetic aortopathy were younger, had fewer cardiometabolic comorbidities, and more often presented with acute dissection or postdissection aneurysm rather than degenerative aneurysm. Prior aortic surgery was substantially more common in the genetic aortopathy group, particularly prior ascending aorta or arch repair. Perioperative mortality, defined as death within 30 days or during the index hospitalization, did not differ after multivariable adjustment between patients with or without genetic aortopathy (4.6% vs 7.0%; adjusted odds ratio, 1.1; 95% CI, 0.57-1.9). Similarly, there were no adjusted differences in odds of any in-hospital complication or in-hospital reintervention, although postoperative vasopressor use (33% vs 27%; adjusted odds ratio, 1.44; 95% CI, 1.1-1.9) and blood transfusion (25% vs 23%; adjusted odds ratio, 1.39; 95% CI, 1.03-1.9) were more common in the genetic aortopathy group. The groups had similar 5-year survival (81% with genetic aortopathy vs 74% without; aHR, 1.02; 95% CI, 0.70-1.5), whereas 2-year reintervention rates were significantly higher in patients with genetic aortopathy (25% vs 13%; aHR, 1.99; 95% CI, 1.4-2.9). Sensitivity analyses in the genetic aortopathy cohort suggested that patients with prior ascending aorta or arch repair tended to have higher rates of in-hospital complications and reinterventions and possibly worse longer-term outcomes, although these associations were not statistically significant after adjustment. The authors concluded that TEVAR appears initially safe in selected individuals with genetic aortopathies, with perioperative outcomes and midterm survival comparable to those in individuals without genetic disease; however, there is a higher need for subsequent reintervention. These findings are limited by the observational design, lack of randomization, absence of a surgical comparator, potential selection bias, incomplete long-term follow-up, and predominance of Marfan syndrome, all of which limit generalizability to other genetic aortopathies.

Clinical Practice Guidelines

American College of Cardiology (ACC)/American Heart Association (AHA)

The 2022 ACC/AHA guideline for the diagnosis and management of aortic disease (Isselbacher et al.) includes the following recommendations related to genetic testing in patients affected by TAD and screening of their family members:

- For patients with aortic root/ascending aortic aneurysms or aortic dissection, obtain a multigenerational family history of TAD, unexplained sudden deaths, and peripheral and intracranial aneurysms [class of recommendation: 1 (strong); level of evidence: B-NR (moderate)].
- In patients with aortic root/ascending aortic aneurysms or aortic dissection and risk factors for hereditary TAD, perform genetic testing to identify pathogenic/likely pathogenic variants [class of recommendation: 1 (strong); level of evidence: B-NR (moderate)].
- For patients with an established pathogenic/likely pathogenic variant in a gene predisposing to hereditary TAD, provide genetic counseling and clinical management that are guided by the specific gene/variant [class of recommendation: 1 (strong); level of evidence: B-NR (moderate)].
- In patients with TAD who have a pathogenic/likely pathogenic variant, perform genetic testing in at-risk biological relatives [e.g., cascade testing; class of recommendation: 1 (strong); level of evidence: B-NR (moderate)].
- In patients with bicuspid aortic valve and either hereditary TAD or phenotypic features concerning for Loeys-Dietz syndrome, obtain a medical genetics evaluation [class of recommendation: 1 (strong); level of evidence: C-LD (limited data)].

American College of Cardiology (ACC)/American Heart Association (AHA)/American Association for Thoracic Surgery (AATS)/American College of Radiology (ACR)/American Stroke Association (ASA)/Society of Cardiovascular Anesthesiologists (SCA)/Society for Cardiovascular Angiography and Interventions (SCAI)/Society of Interventional Radiology (SIR)/Society of Thoracic Surgeons (STS)/Society for Vascular Medicine (SVM)/North American Society for Cardiovascular Imaging (NASCI)

Hiratzka et al. (2010) published consensus guidelines from multiple professional societies that are involved in the care of patients who have or are at risk for thoracic aortic aneurysm or dissection. The guidelines note that identification of an underlying genetic mutation is important in providing care for the patient and at-risk family members. For example, if a patient harbors a mutation in *FBN1*, *TGFBR1*, *TGFBR2*, *COL3A1*, *ACTA2*, or *MYH11*, first-degree relatives should have genetic counseling and testing. Only family members with an inherited genetic mutation should have aortic imaging (level

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of evidence: C). Genetic testing to verify the underlying genetic variant can help identify the best treatment plan. For example, patients with Loeys-Dietz syndrome or a confirmed *TGFRB1* or *TGFBR2* mutation should have yearly magnetic resonance imaging performed from the cerebrovascular circulatory system to the pelvis (level of evidence: B). If there is an aortic diameter of 4.2 cm or greater by ultrasound, surgical repair should be considered (level of evidence: C). Sequencing of the *ACTA2* gene in patients with a family history of thoracic aortic aneurysm or dissection is reasonable, and sequencing of *TGFBR1, TGFBR2*, and *MYH11* in patients with a family and clinical history that is consistent with a particular genetic disease can be considered (level of evidence: B). The authors noted that inherited TAD is often asymptomatic until a life-threatening event occurs, so evaluating at-risk family members can save lives.

Levels of evidence
- A: Multiple populations evaluated; data derived from multiple randomized clinical trials or meta-analyses.
- B: Limited populations evaluated; data derived from a single randomized trial or nonrandomized studies.
- C: Very limited populations evaluated; consensus opinion, case studies, or standard of care.

American Heart Association (AHA)

The AHA (Morris et al., 2024) issued a scientific statement that outlines indications for genetic testing for aortopathy in children. A hereditary TAD panel may be considered for nonsyndromic presentations or for children with prominent systemic connective tissue features to confirm a diagnosis and guide disease-specific cardiovascular and extracardiovascular management. Indications for genetic testing in children with suspected hereditary TAD include the following:
- In a child with a bicuspid aortic valve, testing is indicated if one or more of the following is present:
  - Personal history of aortic or arterial dissection/rupture or spontaneous bowel perforation
  - Features seen in syndromic heritable TAD
  - First-degree family member with a (likely) pathogenic variant in a hereditary TAD gene
  - Family member with a history of aortic or arterial dissection/rupture, aortic aneurysm, or bowel perforation
- In a child with a bicuspid aortic valve, testing may be considered if one or more of the following is present:
  - Ascending aortic z score of ≥ 5
  - Aortic root z score of ≥ 3.5
  - Aortic root or ascending aorta of ≥ 4 cm
  - Aortic root phenotype (aortic root z score greater than ascending aortic z score)
  - Family history of bicuspid aortic valve, coarctation, or hypoplastic left heart syndrome
- In a child without a bicuspid aortic valve, testing is indicated if one or more of the following is present:
  - Personal history of aortic or arterial dissection/rupture or spontaneous bowel perforation
  - Aortic root or ascending aortic z score of ≥ 2 and < 3 and one or more features seen in syndromic hereditary TAD, without another nonhereditary TAD explanation
  - Aortic root or ascending aortic z score of ≥ 3 or dimension of ≥ 4 cm, without another nonhereditary TAD explanation
  - Aortic root or ascending aorta of ≥ 5 cm
  - Multiple clinical features of syndromic hereditary TAD
  - First-degree family member with a (likely) pathogenic variant in a hereditary TAD gene
  - First-degree family member with a history of aortic or arterial dissection/rupture, aortic aneurysm, or bowel perforation

The AHA (Musunuru et al., 2020) issued a scientific statement that identified 11 genes with strong or definitive evidence of association with highly penetrant heritable thoracic aortic aneurysms or dissections, with or without syndromic features (*ACTA2*, *COL3A1*, *FBN1*, *MYH11*, *SMAD3*, *TGFB2*, *TGFBR1*, *TGFBR2*, *MYLK*, *LOX*, and *PRKG1*). An additional eight genes were noted to have significant evidence that supports increased risk (*EFEMP2*, *ELN*, *FBN2*, *FLNA*, *NOTCH1*, *SLC2A10*, *SMAD4*, and *SKI)*. Identification of a pathogenic variant in these genes can provide clinically actionable information regarding aortic disease manifestations, associated conditions, and risk of aortic dissection, dilation, or other vascular disease.

European Association for Cardio-Thoracic Surgery (EACTS)/Society of Thoracic Surgeons (STS)

The EACTS and STS (Czerny et al., 2024) issued guidelines on the diagnosis and treatment of acute and chronic aortic syndromes. The following recommendations for heritable TAD are included:
- Genetic testing is recommended in patients with TAD who are < 60 years of age, have a family history of TAD, have arterial aneurysms in other segments, and have syndromic features [class 1 recommendation (is recommended/is indicated); level of evidence: B (data derived from a single randomized clinical trial or from large, nonrandomized studies)].

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- Testing of family members is recommended by sequencing of only the suspect genetic area [class 1 recommendation (is recommended/is indicated); level of evidence: C (consensus of expert opinion and/or small studies, retrospective studies, and registries)].

Coronary Artery Disease

The evidence is insufficient to support the use of genetic testing, such as PRSs or gene expression testing, for coronary artery disease (CAD). Further studies that include a larger number of individuals and longer follow-up are needed to determine the clinical utility of these tests.

The Põld et al. (2026) parallel-group, double-blinded, randomized controlled trial assessed whether communicating high CAD PRSs influenced cardiovascular risk–related behaviors or cardiometabolic outcomes in overweight adults who were aged 25 to 44 years. Recruitment occurred through primary care practices, and the intervention was delivered by participants' own family physicians, who were trained in risk assessment, counseling, and preventive treatment. Participants were randomized 1:1 to an intervention or control group, with both groups consisting of participants in the highest polygenic risk quintile. Both physicians and control-arm participants were masked to control-arm polygenic risk until the end of follow-up. Overall, 1,020 participants were randomized, with baseline analyses that included 464 participants in the intervention group and 449 in the control group. The mean age was 37.7 years, and 45.5% were women. The baseline behavioral risk was low, including minimal smoking and infrequent alcohol use, and body mass index averaged 27.7 kg/m². The intervention integrated personalized cardiovascular risk estimates that included polygenic risk, displayed through graphical tools, which were discussed in a counseling session. Participants were followed up for 12 months, with in-person baseline and final visits and a remote 6-month visit. Over 12 months, the study failed to demonstrate differences between groups in the primary outcome of body mass index (27.9 ±2.5 kg/m² vs 27.7 ±2.5 kg/m²; p = 0.291). No between-group differences were observed in systolic or diastolic blood pressure, waist circumference, lipid measures, blood glucose, or combined 10-year cardiovascular risk. Self-reported smoking, alcohol consumption, fruit and vegetable intake, and physical activity showed no meaningful between-group differences. Preventive treatment patterns were also similar: 15.5% of intervention-group participants and 19.2% of controls received prescriptions for lipid-lowering or antihypertensive medications, and purchasing patterns did not differ. The incidence rate ratios for lipid-lowering drugs and antihypertensive drugs were 0.93 (95% CI, 0.73-1.18) and 0.97 (95% CI, 0.79-1.21), respectively. The authors concluded that integrating and communicating high polygenic risk for CAD did not lead to improvements in cardiovascular risk factors or sustained behavior change over 12 months. They noted that the young age in the population, low baseline behavioral risk, limited intensity of counseling, and challenges in incorporating novel genetic information into primary care communication may have contributed to the limited effect. The findings were additionally constrained by participant attrition, the absence of intention-to-treat analyses, and the 12-month duration, which may be insufficient to detect gradual behavior change.

The Iribarren et al. (2025) study examined whether the association between low-density lipoprotein cholesterol (LDL-C) and incident coronary heart disease was modified by background polygenic risk in a large, real-world cohort. The investigators conducted a prospective, observational analysis in the Genetic Epidemiology Research on Aging cohort of Kaiser Permanente Northern California (KPNC), using genome-wide data and longitudinal clinical follow-up through December 31, 2022. From an initial 110,226 participants, 47,576 statin-naive adults who were aged 30 to 79 years, without diabetes or prevalent coronary heart disease, were included after extensive exclusions. At baseline, the mean age of the participants was 58 years; 62% were female, and 82% self-identified as being of European ancestry, with smaller proportions identifying as African American (3%), Latino (7%), or Asian (8%). Polygenic risk was assessed using the commercially available CARDIO inCode-Score PRS, which was categorized into low (first quintile), intermediate (quintiles two to four), and high (fifth quintile). LDL-C was measured at baseline and grouped as < 100, 100 to 129, 130 to 159, 160 to 189, and ≥ 190 mg/dL. The primary outcome was incident coronary heart disease, defined as myocardial infarction, coronary revascularization, angina pectoris, or coronary heart disease death. Over a mean follow-up of 13.8 years, 1,678 coronary heart disease events occurred. Age-adjusted coronary heart disease rates were estimated using Poisson regression, and Cox proportional hazards models that were adjusted for age, sex, five principal components of genetic ancestry, body mass index, smoking, and hypertension were used to estimate HRs, with low polygenic risk and an LDL-C of < 100 mg/dL as the reference group. No statistically significant interaction was detected between continuous LDL-C and polygenic risk (p = 0.34) or categorical LDL-C and polygenic risk (p = 0.60). In the low polygenic risk group, coronary heart disease rates remained low until LDL-C reached ≥ 190 mg/dL; severe hypercholesterolemia in this group was associated with an HR of 2.3 (p = 0.06). In the intermediate polygenic risk group, coronary heart disease risk increased steadily with rising LDL-C, with HRs exceeding 2.0 beginning at an LDL-C of 160 mg/dL. In the high polygenic risk group, increased coronary heart disease risk was observed at much lower LDL-C levels, including in participants with an LDL-C of < 100 mg/dL (HR, 1.75; 95% CI, 1.22-2.40; p < 0.0001), with progressively higher risk at increasing LDL-C categories. The combination of high polygenic risk and an LDL-C of ≥ 190 mg/dL was associated with an HR of 3.6. The authors concluded that polygenic risk influences the LDL-C level at which coronary heart disease risk rises, with individuals at high

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polygenic risk exhibiting increased risk, even at LDL-C levels that are traditionally considered low, particularly when severe hypercholesterolemia is present. The findings are limited by the observational design, lack of randomization and masking, potential residual confounding, limited representation of non-European ancestry groups, restriction to insured participants in one health system, absence of genetic assessment for familial hypercholesterolemia, and industry funding and financial relationships that are related to the CARDIO inCode-Score PRS, which may have influenced the interpretation of the findings.

The Liu et al. (2025) systematic review of studies assessed the use of genomic testing in coronary atherosclerosis (CAD), with a focus on its role in early diagnosis, risk stratification, and personalized treatment. The review found that genome-wide association studies and sequencing studies have identified key CAD-associated variants, including *JCAD/KIAA1462*, *GUCY1A3*, *PCSK9*, and *SORT1*, which are implicated in inflammation, lipid metabolism, and vascular function. Evidence from twin and familial studies suggests that genetics account for roughly 40% to 60% of CAD risk. Transcriptomic and epigenomic analyses have also revealed disease-specific expression patterns, DNA methylation signatures, and regulatory noncoding RNAs that may support earlier detection. Despite these advances, the authors noted persistent barriers to clinical adoption, including variability in marker behavior, lack of standardization, and challenges integrating genomic results with traditional diagnostics. They recommended large-scale, prospective studies; development of standardized guidelines; and improved data-integration approaches to support broader implementation.

Naderian et al. (2025) conducted a post hoc 10-year follow-up of the single-center, unblinded, randomized MI-GENES (Myocardial Infarction Genes) clinical trial, in which 207 non-Hispanic White participants, who were aged 45 to 75 years, long-term residents of Olmsted County, Minnesota, and at an intermediate 10-year coronary heart disease risk, were randomized to receive either a Framingham Risk Score alone or an integrated risk score that incorporated a PRS. Overall, 100 participants in the Framingham Risk Score group and 103 in the integrated risk score group completed follow-up, with no loss to follow-up during a median of 9.5 years. All participants were not taking statins at enrollment. Risk disclosure occurred via a structured genetic counseling session, followed by shared decision-making with a preventive clinician. The post hoc analysis relied on electronic health record review to identify major adverse cardiovascular events, using blinded adjudication. The primary outcome was time to first major adverse cardiovascular event, defined as cardiovascular death, nonfatal myocardial infarction, coronary revascularization, or nonfatal stroke. Analyses used Cox proportional hazards models without additional adjustment because of the original randomization, and repeated-measures linear mixed-effects models were applied for lipid and other risk factor trajectories. During follow-up, nine participants in the Framingham Risk Score group and two in the integrated risk score group experienced a major adverse cardiovascular event (HR, 0.20; 95% CI, 0.04-0.94; p = 0.042). More participants in the Framingham Risk Score group underwent diagnostic testing for coronary heart disease, whereas integrated risk score participants had lower rates of ischemia detected during stress testing. Participants who received an integrated risk score had higher statin use during the first 4 years and lower LDL-C for up to 3 years, with additional reductions in non–high-density lipoprotein cholesterol and triglycerides for several years. No significant differences were observed between the two groups in blood pressure, hemoglobin A_{1c}, or weight, although smoking cessation occurred more often in the integrated risk score group. The authors concluded that disclosure of an integrated risk score that included a PRS was associated with lower incidence of major adverse cardiovascular events and lower frequency of coronary heart disease testing, which is an effect that was likely mediated by earlier and more sustained statin use that resulted in lower LDL-C exposure. The findings are limited by the modest sample size, small number of events, post hoc nature of the analysis, lack of masking, and restricted demographic diversity. The results may not be generalizable beyond this single-center population.

The Park et al. (2024) prospective, observational cohort study examined whether adding a CAD PRS to established clinical risk models could better inform statin initiation or deferral in primary prevention. A national biobank was used, and the analysis included 311,799 participants who were aged 40 to 73 years; were free of atherosclerotic cardiovascular disease, diabetes, chronic kidney disease, and lipid-lowering therapy at baseline; and had an available CAD PRS. Participants were assigned to cohorts that were categorized as statin indicated (SI), statin indication unclear (SU), or statin not indicated (SN), according to the 2021 European Society of Cardiology and 2019 ACC/AHA guidelines. The primary outcome was a major coronary event, defined as acute myocardial infarction, coronary revascularization, or CAD death, and the secondary outcome was guideline-defined atherosclerotic cardiovascular disease events. During a median follow-up of 11.9 years (IQR, 11.2-12.6 years), 8,196 major coronary events occurred. Analyses used recalibrated European SCORE2 (Systematic Coronary Risk Evaluation 2) and U.S. PCE (Pooled Cohort Equation) models and accounted for competing risk of death. Adding the CAD PRS mainly affected risk stratification in the SI and SU cohorts. In the SU cohort, 18% (European SCORE2) and 12% (U.S. PCE) had major coronary event risk that was similar to or higher than the average risk in participants in the SI cohort; 16% and 12% of participants in the SI cohort had a risk comparable to or lower than that in those in the SU cohort. The lifetime risk of major coronary events ranged from 37.4% (95% CI, 29.3%-45.8%) in participants in the SI cohort who had a high CAD PRS to 1.3% (95% CI, 1.1%-1.5%) in participants in the SN cohort who had a low CAD PRS. For atherosclerotic cardiovascular disease events, adding the CAD PRS improved discrimination among participants in the SI and SU cohorts. Net reclassification improvement for atherosclerotic

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cardiovascular disease events was 13.6% (95% CI, 11.8%-15.5%) and 14.7% (95% CI, 13.1%-16.3%) in the SI cohort, 10.8% (95% CI, 9.6%-12.0%) and 15.3% (95% CI, 13.2%-17.5%) in the SU cohort, and 0.9% (95% CI, 0.6%-1.3%) and 3.6% (95% CI, 3.0%-4.2%) in the SN cohort for the European and U.S. models, respectively. The authors concluded that the CAD PRS may support statin initiation or deferral in individuals who are classified as SI or SU but offers little clinical value in those for whom statins are not indicated under current models. These findings are limited by the study's observational design, reliance on risk model recalibration, and absence of randomized treatment comparisons.

The Iribarren et al. (2024a) observational study used data from a large, contemporary cohort in KPNC to evaluate whether the CARDIO inCode-Score, a 12–single-nucleotide polymorphism (SNP) PRS, was associated with incident coronary heart disease over long-term follow-up and whether genetic risk further stratified participants in ACC/AHA PCE risk categories. The study included 63,070 participants who were aged 30 to 74 years and did not have prior coronary heart disease; participants were recruited from the GERA (Genetic Epidemiology Research on Adult Health and Aging) cohort through self-administered questionnaires and linked clinical data. The cohort was predominantly female and largely of European ancestry, with smaller African American, Latino, and Asian groups; most participants had at least a college education. Participants were followed up for up to 20.6 years, during which 3,289 incident coronary heart disease events occurred. Across the full cohort, each SD increase in the PRS was associated with an aHR of 1.18 (95% CI, 1.14-1.22), and participants in the highest vs lowest quintile had an aHR of 1.66 (95% CI, 1.49-1.86). The results were similar in men and women and among European participants and minorities combined. Subgroup estimates for minority groups individually had wider CIs. The predictive association was strongest during the first 5 years of follow-up. Incorporation of the PRS into a model that already contained PCE variables increased the C-statistic from 0.747 to 0.751 ($p < 0.0001$), yielded a net reclassification improvement of 2.4 for the entire cohort, and produced greater reclassification (9.7) in those at intermediate PCE risk. Participants at borderline or intermediate PCE risk but with high genetic risk experienced absolute event rates that were similar to those in participants at higher clinical risk categories. The authors concluded that polygenic risk provided additional predictive information for incident coronary heart disease and improved risk reclassification, particularly in participants with borderline or intermediate estimated clinical risk. The authors noted limitations related to generalizability, including that the cohort consisted of insured health system members who had high educational attainment. They also described the lack of recalibration of the PCE, reduced predictive performance in African American and Asian participants due to the European-derived genetic panel, and absence of lipoprotein(a) measurements. The authors disclosed financial relationships that involve development of the CARDIO inCode-Score commercial test.

Iribarren et al. (2024b) conducted a large, observational cohort study that used data from GERA and examined whether lifestyle factors and a clinically validated 12-SNP PRS independently or jointly predicted incident coronary heart disease. The study included 60,568 KPNC members who were aged 30 to 79 years; 67% were female, and 82% identified as White. Participants completed a baseline questionnaire between 2007 and 2009, and the cohort was followed up for a mean of 14 years for incident coronary heart disease, which was identified from hospital diagnoses, coronary revascularization procedures, or coronary heart disease–related deaths. Lifestyle exposures included smoking status, adherence to a Mediterranean diet pattern, and meeting U.S. physical activity recommendations, each determined by self-report. The analysis used Cox regression adjusted for demographic factors, genetic ancestry, education, cholesterol-lowering drug use, and family history of heart attack. No blinding or randomization occurred, and all assessments were based on existing clinical or administrative data. The authors analyzed lifestyle factors individually and as a combined three-level lifestyle score. No statistically significant interactions were found between continuous PRS and any individual lifestyle factor. During follow-up, 3,159 coronary heart disease events occurred. Former smoking and current smoking were associated with a 1.14-fold and 1.48-fold higher hazard of coronary heart disease, respectively, and adhering to a Mediterranean diet and meeting physical activity recommendations were associated with 14% and 15% lower hazard. Compared with participants in the lowest polygenic risk group, those in quintiles two to four and quintile five had a 1.27-fold and 1.68-fold higher hazard, respectively. Participants with the least favorable lifestyle and high genetic risk had up to a 3.4-fold higher risk relative to those with all three favorable lifestyle factors and low genetic risk. Moving from no favorable lifestyle factors to all three favorable factors was associated with a 52% lower rate of coronary heart disease in participants with high genetic risk. The numbers needed to treat for a hypothetical lifestyle intervention were 34 for low genetic risk, 24 for intermediate genetic risk, and 19 for high genetic risk. The authors concluded that lifestyle and polygenic risk have additive effects on incident coronary heart disease and that individuals with high polygenic risk may derive greater absolute benefit from favorable lifestyle practices. Limitations that were described by the authors include limited generalizability due to drawing the study population from a single integrated health system; a PRS that was developed primarily from European ancestry data; and reliance on self-reported lifestyle behaviors that may not remain stable over time. The authors disclosed financial relationships that involve the PRS.

Nurmohamed et al. (2024) conducted a prospective, single-center cohort study to evaluate whether a CAD PRS was associated with long-term changes in coronary plaque and the prevalence of high-risk plaque. Recruitment occurred in a single academic medical center, and participants had no prior history of CAD at baseline. Participants underwent baseline

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coronary computed tomography angiography between 2008 and 2014 and were invited for repeat imaging after approximately 10 years. Plaque was quantified using an artificial intelligence–based algorithm. The primary outcomes were changes in percent atheroma volume and noncalcified plaque, with secondary outcomes that included changes in calcified plaque and the presence of high-risk plaque, which was defined by low-density, noncalcified plaque with positive remodeling. A total of 288 participants consented to genotyping, completed both scans, and had plasma available. The cohort had a mean age of 58 years, was 60% male, and was predominantly of White European ancestry. PRSs were calculated from a multiancestry, genome-wide risk score of 1.2 million variants, which was categorized into low (first quintile), intermediate (second to fourth quintiles), and high (fifth quintile). Analyses used linear mixed-effects models and logistic regression, with adjustment for age, sex, genetic ancestry, and conventional risk factors. Participants with a high PRS had substantially greater plaque burden at baseline, including more than a five-fold higher percent atheroma volume than those with a low PRS (10.4% vs 1.9%). During a median 10.2-year interval, polygenic risk remained associated with accelerated plaque progression. Each 1-SD increase in the PRS corresponded to a 0.69% increase in percent atheroma volume progression, and high-risk participants had 2.75% greater progression than those with a low PRS. Polygenic risk was also associated with higher progression of both noncalcified and calcified plaque and a lower likelihood of noncalcified plaque regression. High-risk genetic groups had a greater likelihood of high-risk plaque at both baseline (odds ratio, 2.85) and follow-up (odds ratio, 6.16). During follow-up, 12.8% of participants experienced a major adverse cardiovascular event, and those with high or intermediate polygenic risk had higher event rates; however, when polygenic risk and baseline plaque features were modeled together, plaque burden and high-risk plaque, rather than polygenic risk, remained the independent predictors of events. The authors concluded that polygenic risk is strongly associated with long-term coronary plaque progression and high-risk plaque formation in individuals with suspected CAD. The study's findings are limited by its observational design, single-center setting, and focus on participants of predominantly European ancestry. The authors noted additional limitations, including potential differences in scanner technology over the long imaging interval; exclusion of revascularized vessels (which may underestimate progression); limited power for cardiovascular event analyses; and potential treatment differences, which were influenced by baseline imaging results. The long follow-up interval may also have introduced variability in plaque characterization despite analytic adjustments. Overall, the findings are constrained by the lack of randomization and absence of a comparison group beyond genetic risk strata.

Li et al. (2024) performed a large observational study to evaluate whether a PRS for CAD could be integrated with the SCORE2 clinical risk tool, which is recommended by the European Society of Cardiology to refine prediction of cardiovascular disease. The analysis used longitudinal data from 432,981 individuals of European ancestry, who were primarily middle aged or older, in the UK Biobank and replicated findings in 10,757 individuals from the Framingham and ARIC (Atherosclerosis Risk in Communities) cohorts. The study compared cardiovascular disease odds across tenths of the PRS distribution and across SCORE2 clinical risk strata. PRSs were generated using genome-wide variant data and adjusted for demographic variables. SCORE2-predicted absolute risk was derived using age, sex, systolic blood pressure, non–high-density lipoprotein cholesterol, and smoking status. Cardiovascular disease was defined using diagnostic codes. Follow-up for incident events occurred in the framework of each contributing cohort. Individuals with existing cardiovascular disease were excluded for incident analyses. The primary findings showed that cardiovascular disease odds ratios that were associated with each PRS tenth (referred to as PRS factors) were stable across subgroups that were defined by traditional clinical risk factors and SCORE2 risk categories. Cardiovascular disease odds increased from 0.63 in the lowest PRS factor to 1.72 in the highest PRS factor. The authors found no significant interactions between SCORE2 categories and the PRS. A multiplicative model, SCORE2 × PRS factor, modestly improved discrimination, increasing the C-index by 0.9% ($p = 1.6e^{-12}$) and the net reclassification index by 0.063 (95% CI, 0.059-0.067). Among 145,337 individuals at an intermediate SCORE2 risk, 9.55% (n = 13,886) were reclassified upward to high risk; these individuals experienced an incident cardiovascular disease rate of 8.08%, nearly double the 4.08% in those who remained at intermediate risk. The authors concluded that polygenic and clinical risks act independently and that the PRS factor can refine absolute risk estimates that are derived from SCORE2. The limitations noted by the authors include the exclusive use of a CAD PRS rather than a combined CAD and stroke score; restriction to individuals of European ancestry; and potential limited generalizability across populations or age groups. The study lacked randomization, masking, and a controlled comparative design. The short descriptions of follow-up and absence of detailed information on missing data or loss to follow-up also constrain assessment of bias. The small absolute improvements in predictive performance across the population reflect the limited effect size of PRSs for most individuals.

Hayes (2024) published a Precision Medicine Research Brief to summarize the volume of publications and to determine whether there is adequate published, peer-reviewed literature to evaluate the evidence related to the PrecisionCHD test (Cardio Diagnostics Inc.) to detect coronary heart disease. Hayes did not identify any abstracts that address the test's clinical utility or evaluate the test's performance. Hayes concluded that there is no/unclear support for the test in clinical practice guidelines and position statements because no relevant position statements or guidelines were identified that explicitly addressed the use of the PrecisionCHD test or DNA analysis to detect coronary heart disease.

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Hayes (2024) published a Precision Medicine Research Brief to summarize the volume of publications and to determine whether there is adequate published, peer-reviewed literature to evaluate the evidence related to the Epi+Gen CHD test (Cardio Diagnostics Inc.) to predict the 3-year risk of symptomatic coronary heart disease. Hayes did not identify any abstracts that address the test's clinical utility or evaluate the test's performance. Hayes concluded that there is no/unclear support for the test in clinical practice guidelines and position statements because no relevant position statements or guidelines were identified that explicitly addressed the use of the Epi+Gen CHD test or the use of DNA biomarkers to assess the risk of coronary heart disease/coronary events.

The Busby et al. (2023) study evaluated whether ancestry-specific PRSs for CAD enhance clinical atherosclerotic cardiovascular disease risk assessment when used as risk enhancers. The investigators developed 152 candidate PRSs, then validated and tested the best-performing scores across independent cohorts from the UK Biobank, MESA (Multi-Ethnic Study of Atherosclerosis), and ARIC study. Overall, 29,389 individuals were included for PRS development and validation, and an independent PCE evaluation in 9,691 individuals, with complete clinical covariates, was used. Individuals were adults who were between the ages of 35 and 84 years, with representation across African, Native American, East Asian, European, and South Asian genetic ancestry groups, although non-European sample sizes were smaller. Across ancestry groups, each SD increase in the PRS was associated with a 47% increase in the odds of CAD among individuals of Native American ancestry (odds ratio, 1.47; 95% CI, 1.08-2.01) and an 81% increase among individuals of South Asian ancestry (odds ratio, 1.81; 95% CI, 1.31-2.50), with these associations being stronger than those observed using three previously published PRSs. To assess clinical impact, the authors defined ancestry-specific PRS thresholds corresponding to an approximate two-fold increase in CAD risk and identified 12% to 24% of individuals as being at a high genetic risk, depending on ancestry. In the PCE testing cohort, 16% of individuals with borderline or intermediate 10-year atherosclerotic cardiovascular disease risk had this two-fold PRS risk factor. Among these individuals, there were 64% more coronary heart disease events and 47% more atherosclerotic cardiovascular disease events compared with those without the PRS risk factor. Reclassification analyses showed that adding the CAD PRS as a risk enhancer yielded a net reclassification improvement of 13.14% (95% CI, 9.23%-17.06%) for coronary heart disease and 10.70% (95% CI, 7.35%-14.05%) for atherosclerotic cardiovascular disease. In models that adjusted for all PCE covariates, the two-fold PRS risk factor remained associated with CAD (odds ratio, 2.03; 95% CI, 1.49-2.76). When PRSs were directly integrated into the PCE, smaller but statistically significant categorical net reclassification improvements were observed for CAD (4.31%; 95% CI, 1.85%-6.78%) and atherosclerotic cardiovascular disease (2.90%; 95% CI, 0.61%-5.18%). The authors concluded that validated, ancestry-specific CAD PRSs function as effective risk enhancers for atherosclerotic cardiovascular disease assessment, particularly for reclassifying individuals with borderline or intermediate clinical risk. The findings are limited by the observational design, lack of randomization and masking, relatively small non-European sample sizes, continental-level ancestry grouping, and uncertainty regarding generalizability outside the included populations. Well-designed, larger, comparative studies, with refined global representation, are needed. All authors disclosed an employment relationship with Allelica, Inc.

The Patel et al. (2023) study developed and validated a multiancestry PRS for CAD, termed GPS Mult, with the objective of improving risk prediction across diverse ancestral groups. The investigators aggregated genome-wide association study summary statistics for CAD and 10 related cardiometabolic traits from more than 269,000 CAD cases and over 1,178,000 controls who spanned African, East Asian, European, Hispanic, and South Asian ancestries. With a two-layer modeling approach, ancestry-stratified and trait-specific polygenic scores were constructed and combined through logistic regression in 116,649 UK Biobank individuals of European ancestry; performance was evaluated in an independent UK Biobank validation cohort of 325,991 individuals and external cohorts, including the Million Veteran Program and Genes & Health. In the UK Biobank European ancestry validation cohort, GPS Mult was strongly associated with prevalent CAD, with an odds ratio per SD increase of 2.14 (95% CI, 2.10-2.19; $p < 0.001$), which remained similar after adjustment for clinical risk factors (odds ratio/SD, 2.07; 95% CI, 2.02-2.13). GPS Mult was also associated with incident CAD events during a median follow-up of 12.0 years, with an HR per SD of 1.73 (95% CI, 1.70-1.76; $p < 0.001$) compared with 1.49 (95% CI, 1.46-1.52) for a previously published score. Across external validation cohorts, GPS Mult demonstrated associations with prevalent CAD, with an odds ratio/SD of 1.25 (95% CI, 1.21-1.29) in individuals of African ancestry; 1.72 (95% CI, 1.69-1.75) in European ancestry; 1.61 (95% CI, 1.53-1.70) in Hispanic ancestry; and 1.83 (95% CI, 1.69-1.99) in South Asian ancestry. GPS Mult consistently outperformed prior polygenic scores. When integrated with established clinical risk estimators, GPS Mult improved discrimination, increasing the C-statistic from 0.739 (95% CI, 0.735-0.744) for the PCE alone to 0.763 (95% CI, 0.759-0.768), and improved categorical net reclassification by 7.0% at a 7.5% 10-year risk threshold. The authors concluded that large-scale integration of multiancestry and multitrait genetic data substantially improves polygenic prediction of CAD and enhances risk stratification beyond clinical risk factors alone, particularly at the extremes of genetic risk. The limitations documented by the study include reduced predictive performance in individuals of African ancestry due to underrepresentation in discovery genome-wide association studies; relatively small numbers of incident events in non-European ancestry groups in the UK Biobank; potential selection and survivorship bias related to UK Biobank recruitment at ages 40 to 69 years; and reliance on registry and self-reported data for outcome ascertainment. The findings are limited by the observational design. Further validation in younger and more diverse

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populations is needed before widespread clinical implementation. The authors disclosed multiple financial conflicts of interest that are related to industry relationships and are among several investigators.

Boccanelli and Scardovi (2023) reported findings from the PRE-DETERMINE cohort study, which evaluated whether biomarkers and ECG measures can help identify individuals at an increased risk of sudden death. The analysis examined the prognostic value of genome-wide polygenic scores for CAD (GPSCAD) in individuals with intermediate-risk, stable CAD who did not have severe systolic dysfunction or an indication for an implantable cardioverter-defibrillator. During a mean follow-up of 8 years, individuals in the highest GPSCAD decile had a higher absolute risk (8.0% vs 4.8%; $p < 0.005$) and relative risk (29% vs 16%; $p < 0.0003$) of sudden death than the rest of the cohort. No association was observed between the highest GPSCAD decile and other cardiac or noncardiac causes of death. The authors concluded that these findings support only theoretical estimates of the potential benefit of implantable defibrillators in individuals with chronic CAD and moderately reduced left ventricular function and emphasized the need for additional research.

Sun et al. (2021) evaluated the clinical utility of PRSs for cardiovascular disease, examining both coronary heart disease and stroke, and assessed implications for guideline-directed statin therapy. Data from 306,654 UK Biobank participants who did not have a history of cardiovascular disease and were not receiving lipid-lowering therapy were used, and the authors found that adding PRSs to conventional risk factors modestly improved risk prediction. The C-index measure of risk discrimination for a model based on conventional predictors was 0.710 (95% CI, 0.703-0.717), increasing by 0.012 (95% CI, 0.009-0.015) with PRSs, with continuous reclassification improvements of 10% for cases and 12% for noncases. Population-level modeling that used data from 2.1 million participants in the Clinical Practice Research Datalink suggests that universal PRS assessment in adults aged 40 to 75 years could prevent one additional cardiovascular disease event per approximately 5,750 individuals screened under current UK guideline treatment thresholds. Targeted PRS assessment in individuals with intermediate 10-year cardiovascular disease risk (5% to < 10%) could prevent one additional event per approximately 340 individuals screened and yield a 7% greater reduction in cardiovascular disease events than conventional risk prediction alone. The projected benefit of adding PRSs exceeded that of incorporating C-reactive protein by approximately 1.5-fold. Because the study population consisted solely of middle-aged participants of European ancestry in the UK, the generalizability of findings is limited. The authors recommended further evaluation of diverse screening strategies, inclusion of individuals from varied ethnic and geographic backgrounds, and assessment of economic and psychological considerations related to integrating genetic risk prediction into cardiovascular disease prevention.

The Mosley et al. (2020) retrospective cohort study assessed whether PRSs improved prediction of coronary heart disease events compared with guideline-recommended clinical risk equations. The analysis included 4,847 White European adults from the ARIC study (mean age, 62.9 years; SD, 5.6 years) and 2,390 patients from the MESA study (mean age, 61.8 years; SD, 9.6 years). Each patient's PRS was calculated using weighted allele dosages for 6,630,149 SNPs. Ten-year coronary heart disease risk prediction from 1996 to 2015 was evaluated against the 2023 ACC/AHA pooled cohort equations using model discrimination, calibration, and net reclassification improvement. Coronary heart disease events occurred in 14.4% of the ARIC patients (n = 696) and 9.5% of the MESA patients (n = 227) over a median 15.5-year follow-up. PRS was significantly associated with 10-year coronary heart disease incidence in both cohorts, with HRs of 1.24 (95% CI, 1.15-1.34) in ARIC and 1.38 (95% CI, 2.21-1.58) in MESA per SD increase. However, the addition of PRS did not meaningfully improve discrimination, calibration, or reclassification beyond conventional predictors. The authors concluded that PRS may not enhance coronary heart disease risk prediction in a general, White, middle-aged population.

Dikilitas et al. (2020) examined the association between restricted and genome-wide PRSs and coronary heart disease across three major U.S. ancestral groups in the eMERGE cohort, which includes 99,185 DNA samples linked to electronic health records. The analysis included 45,645 individuals of European ancestry; 7,597 of African ancestry; and 2,493 of Hispanic ethnicity. Two restricted PRSs (28- and 50-variant panels) and two genome-wide PRSs (1.7M and 6.6M variants) that were developed from European-ancestry cohorts were evaluated. During a median follow-up of 11.1 years, 2,652 coronary heart disease events occurred. Genome-wide PRSs demonstrated stronger associations with coronary heart disease than restricted scores, with the 1.7M-variant genome-wide PRS showing the highest performance across all three groups. HRs per SD increase were 1.53 (95% CI, 1.46-1.60) in European-ancestry, 1.53 (1.23-1.90) in Hispanic-ethnicity, and 1.27 (1.13-1.43) in African-ancestry individuals. Associations were similar between European ancestry and Hispanic ethnicity (p interaction = 0.77) but significantly attenuated in African ancestry (p interaction = 2.9×10^{-3}). The authors reported that PRS associations in European-ancestry individuals were consistent with those in prior studies, comparable in Hispanic-ethnicity individuals, and substantially weaker in African-ancestry individuals. They concluded that genome-wide PRSs outperform restricted PRSs, with the 1.7M-variant genome-wide PRS showing the strongest association with coronary heart disease in all groups; however, differences in variant frequency and genetic architecture across ancestries limit cross-population generalizability. They noted the potential clinical utility for coronary heart disease

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risk assessment but emphasized the need for ancestry-specific PRSs, suggesting that genome-wide PRSs may serve as an interim option for individuals of African ancestry.

Iribarren et al. (2018) evaluated the clinical utility of multilocus genomic risk profiling in participants of Latino (n = 4,349), East Asian (n = 4,804), or African (n = 2,089) ancestry, using data from the GERA cohort of 110,266 adult KPNC members. Two genomic risk scores, based on 12 and 51 SNPs, along with the Framingham Risk Score, were used to estimate 10-year coronary heart disease risk. During a median follow-up of 8.7 years, 450 coronary heart disease events occurred, including 95 among participants of African ancestry, 316 among Latino participants, and 39 among East Asian participants. After adjustment for principal components and clinical risk factors, the 12-SNP score demonstrated an independent association with coronary heart disease, with the highest tertile demonstrating a particularly elevated risk among African American participants when combined with the Framingham score. The 51-SNP score demonstrated an independent association only in the Latino group. Incorporation of the Framingham score led to only modest improvements in risk classification across all groups. The authors concluded that routine use of genomic testing for cardiovascular risk assessment is not currently warranted but noted that genomic risk scores that are validated in European populations also appear relevant for African American, Latino, and, to a lesser extent, East Asian populations. They suggested that individuals at an intermediate clinical risk may benefit from additional assessment using genomic risk scores.

Iribarren et al. (2016) evaluated the clinical utility of genomic risk scores for coronary heart disease in 51,954 individuals of European ancestry, using data from the GERA cohort of 110,266 adult KPNC members. They developed four genomic profiles that contained eight to 51 SNPs based on known genetic variants. During a mean follow-up of 5.9 years, 1,864 coronary heart disease events occurred, and all four SNP-based models demonstrated linear associations with coronary heart disease risk. The HRs for the 8-, 12-, 36-, and 51-SNP panels were 1.21, 1.20, 1.23, and 1.23, respectively. Incorporating genomic risk scores improved overall risk classification by 5% for the 8-, 12-, and 36-SNP profiles and by 4% for the 51-SNP profile. Among individuals categorized as intermediate risk by the Framingham score, net reclassification improvement was 9% for the 8- and 12-SNP profiles and 7% for the 36- and 51-SNP profiles. With this targeted approach, preventing one coronary heart disease event would require treating 36 individuals with statins in the 8- and 12-SNP groups, 41 in the 36-SNP group, and 43 in the 51-SNP group.

Khera et al. (2016) analyzed data from four cohorts (e.g., ARIC study, Women's Genome Health study, Malmö Diet and Cancer study, and BioImage study groups), which comprised 55,685 individuals of White European ancestry, to assess the extent to which healthy behaviors mitigate the genetic risk of CAD. Across the cohorts, the individuals had a mean age of 58 years, and 75% were female. Overall, 42% had baseline hypertension, 6.5% had diabetes, and 25% had a family history of CAD, with an average body mass index of 26 kg/m^2. Additional lipid-related risk factors and medication use were reported for each cohort. Healthy lifestyle behaviors (e.g., regular physical activity, nonsmoking status, healthy diet) were combined into a lifestyle score, while a genomic risk score was derived using up to 50 SNPs weighted by established effect sizes. The genomic risk score was a strong predictor of coronary heart disease events; individuals in the highest genetic risk category had a 91% higher relative risk than those in the lowest category. Although family history was also associated with coronary heart disease, its predictive strength was lower than that of the genomic score. LDL-C levels showed modest associations with coronary heart disease events, and genetic risk categories were not associated with other cardiometabolic risk factors or ACC risk modeling. Unfavorable lifestyle factors showed strong correlations with coronary heart disease events. When lifestyle was examined within genetic risk strata, individuals with a favorable lifestyle had substantially lower coronary heart disease risk (45% lower in the low genomic risk group, 47% lower in the intermediate group, and 46% lower in the high-risk group). Conversely, unfavorable lifestyle factors were correlated with an increased coronary heart disease risk, even in those with low genetic susceptibility. After adjustment for traditional risk factors, the protective effect of a favorable lifestyle remained statistically significant across all groups. These findings suggest that adherence to healthy lifestyle behaviors significantly reduces the risk of CAD regardless of genetic risk level.

Clinical Practice Guidelines

American Heart Association (AHA)

In a 2025 scientific statement (Hull et al.), the AHA addresses the growing availability of direct-to-consumer (DTC) genetic tests for cardiovascular disease. The statement concludes that evidence is insufficient to support their use in routine clinical care. The authors highlighted concerns related to limited oversight and regulation, variability in testing methods and scope, and the absence of standardized results reporting and genetic counseling, all of which may create confusion for both patients and clinicians. They emphasized the need for continued development of industry-wide standards for DTC genetic testing.

A 2022 AHA scientific statement (O'Sullivan et al.) discusses the use of PRSs for cardiovascular disease, noting that large genome-wide association studies support the polygenic nature of cardiometabolic conditions and have identified

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numerous associated single-nucleotide variants. PRSs are increasingly offered by academic institutions and DTC laboratories to research participants and patients. While the authors highlight potential clinical applications, they emphasize important limitations, including the variable incorporation of rare and low-frequency variants, which contribute substantially to heritable disease risk, and limited transferability of PRSs across populations and ethnic groups. The AHA calls for randomized clinical trials that include younger adults and children to assess clinical utility, incremental value beyond traditional risk scores, and effects on treatment decisions and outcomes. The statement also underscores potential harms, such as inequitable benefits across populations, disparities in access, misinterpretation or misuse of PRSs, and risks related to genetic data security, insurance coverage, and health care costs.

The AHA's 2020 scientific statement on genetic testing for inherited cardiovascular disease (Musunuru et al.) notes that patients with extremely high PRSs may face a substantially elevated risk of complex cardiovascular disease compared with the general population. The statement emphasized that the clinically utility of this information, including its potential to inform medical management, remains uncertain.

American Heart Association (AHA)/American College of Cardiology (ACC)

In a joint report (Williams et al., 2025), the AHA and ACC identify personalized treatment plans, based on genetic characteristics, to further refine therapeutic strategies in chronic coronary disease as an area for further research.

American Heart Association (AHA)/American College of Cardiology (ACC)/American College of Clinical Pharmacy (ACCP)/American Society for Preventive Cardiology (ASPC)/National Lipid Association (NLA)/Preventive Cardiovascular Nurses Association (PCNA)

In a joint report (Virani et al., 2023), the AHA, ACC, ACCP, ASPC, NLA, and PCNA advise that further research is needed to assess the use of genomics to improve risk assessment and treatment approaches in diverse populations of patients with chronic coronary disease.

European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS)

In an expert consensus statement on genetic testing for cardiac disease (Wilde et al., 2022), the EHRA, HRS, APHRS, and LAHRS note that a widespread contribution of polygenic risk to CAD susceptibility has been demonstrated. Research has indicated that genetic predisposition to CAD may be useful for risk prediction, but the predictive utility of PRSs for CAD are debated, and such scores are not routinely used in clinical practice.

United States Preventive Services Task Force (USPSTF)

The USPSTF recommendations on the use of nontraditional risk factors in coronary heart disease risk assessment do not address genetic/genomic markers (Curry et al., 2018).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Laboratories that perform genetic tests for cardiac disease are regulated under the Clinical Laboratory Improvement Amendments act of 1988. More information is available at: http://www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm124105.htm. (Accessed March 12, 2026)

Refer to the following website for a list of nucleic acid–based tests/platforms that have been cleared or approved by the FDA's Center for Devices and Radiological Heath: https://www.fda.gov/medical-devices/in-vitro-diagnostics/nucleic-acid-based-tests. (Accessed March 12, 2026)

References

Abood Z, Jan MF, Zlochiver V, et al. Clinical interpretation of genetic variants in the evaluation and management of thoracic aortic aneurysm and dissection. Am J Med. 2024 Sep;137(9):880-887.e2.

Alfares AA, Kelly MA, McDermott G, et al. Results of clinical genetic testing of 2,912 probands with hypertrophic cardiomyopathy: expanded panels offer limited additional sensitivity. Genet Med. 2015 Nov;17(11):880-888. Erratum in: Genet Med. 2015 Apr;17(4):319.

Proprietary Information of UnitedHealthcare. Copyright 2026 United HealthCare Services, Inc.

Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline 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 on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2018 Oct;72(14):e91-e220. Erratum in: J Am Coll Cardiol. 2018 Oct;72(14):1760.

Bariani R, Rigato I, Cason M, et al. Genetic background and clinical features in arrhythmogenic left ventricular cardiomyopathy: a systematic review. J Clin Med. 2022 Jul;11(15):4313.

Bermudez-Jimenez FJ, Protonotarios A, García-Hernández S, et al. Phenotype and clinical outcomes in desmin-related arrhythmogenic cardiomyopathy. JACC Clin Electrophysiol. 2024 Jun;10(6):1178-1190.

Bjelic M, Goldenberg I, Younis A, et al. Risk prediction in male adolescents with congenital long QT syndrome: implications for sex-specific risk stratification in potassium channel-mediated long QT syndrome. J Am Heart Assoc. 2024 Feb;13(3):e028902.

Boccanelli A and Scardovi AB. Sudden death in ischemic heart disease: looking for new predictors: polygenic risk. Eur Heart J Suppl. 2023 Apr;25(Suppl B):B31-B33. Erratum in: Eur Heart J Suppl. 2024 Aug;25(Suppl B):B177.

Busby GB, Kulm S, Bolli A, et al. Ancestry-specific polygenic risk scores are risk enhancers for clinical cardiovascular disease assessments. Nat Commun. 2023 Nov;14(1):7105.

Cabrera-Romero E, Ochoa JP, Barriales-Villa R, et al. Penetrance of dilated cardiomyopathy in genotype-positive relatives. J Am Coll Cardiol. 2024 Apr;83(17):1640-1651.

Charron P, Carrier L, Dubourg O, et al. Penetrance of familial hypertrophic cardiomyopathy. Genet Couns. 1997;8(2):107-114.

Chen L, Hu Y, Saguner AM, et al. Natural history and clinical outcomes of patients with *DSG2*/*DSC2* variant-related arrhythmogenic right ventricular cardiomyopathy. Circulation. 2025 Apr;151(17):1213-1230.

Christian S, Cirino A, Hansen B, et al. Diagnostic validity and clinical utility of genetic testing for hypertrophic cardiomyopathy: a systematic review and meta-analysis. Open Heart. 2022 Apr;9(1):e001815.

Cirino AL, Harris SL, Murad AM, et al. The uptake and utility of genetic testing and genetic counseling for hypertrophic cardiomyopathy: a systematic review and meta-analysis. J Genet Couns. 2022 Dec;31(6):1290-1305.

Conte G, Bergonti M, Probst V, et al. Atrial arrhythmias in inherited arrhythmia syndromes: results from the TETRIS study. Europace. 2024 Dec;26(12):euae288.

Curry SJ, Krist AH, Owens DK, et al. Risk assessment for cardiovascular disease with nontraditional risk factors: US Preventive Services Task Force recommendation statement. JAMA. 2018 Jul;320(3):272-280.

Czerny M, Grabenwöger M, Berger T, et al. EACTS/STS guidelines for diagnosing and treating acute and chronic syndromes of the aortic organ. Ann Thorac Surg. 2024 Jul;118(1):5-115.

Dal Ferro M, Paldino A, Gregorio C, et al. Impact of DCM-causing genetic background on long-term response to cardiac resynchronization therapy. JACC Clin Electrophysiol. 2024 Jul;10(7 Pt 1):1455-1464.

de Santana Santos E, da Costa Kuhn G, Cunha de Almeida AG, et al. Genetic, clinical, and sociodemographic profile of individuals with diagnosis or family history of hypertrophic cardiomyopathy: insights from a prospective cohort. Genes (Basel). 2025 Sep;16(9):1100.

de Uña-Iglesias D, Ochoa JP, Monserrat L, et al. Clinical relevance of the systematic analysis of copy number variants in the genetic study of cardiomyopathies. Genes (Basel). 2024 Jun;15(6):774.

DePaolo J, Biagetti G, Judy R, et al. Polygenic scoring for detection of ascending thoracic aortic dilation. Circ Genom Precis Med. 2024 Oct;17(5):e004512.

DePaolo J, Zamirpour S, Abramowitz S, et al. Predicting thoracic aortic dissection in a diverse biobank using a polygenic risk core. JACC Adv. 2025 May;4(5):101743.

Dikilitas O, Schaid DJ, Kosel ML, et al. Predictive utility of polygenic risk scores for coronary heart disease in three major racial and ethnic groups. Am J Hum Genet. 2020 May;106(5):707-716.

Doundoulakis I, Pannone L, Chiotis S, et al. *SCN5A* gene variants and arrhythmic risk in Brugada syndrome: an updated systematic review and meta-analysis. Heart Rhythm. 2024 Oct;21(10):1987-1997.

Erez E, Acuna Higaki AR, Cupo M, et al. Clinical effectiveness of genetic testing guidelines in patients with thoracic aortic aneurysms. J Thorac Cardiovasc Surg. 2025 Sep;170(3):670-677.e3.

Farkas-Sütő KA, Grebur K, Mester B, et al. Electrocardiogram features of left ventricular excessive trabeculation with preserved cardiac function in light of cardiac magnetic resonance and genetics. J Clin Med. 2024 Oct;13(19):5906.

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García-Cano L, Miguel Martín-Torres J, García-Fernández A, et al. Prognostic impact of the findings of the genetic test in left dominant arrhythmogenic cardiomyopathy. Int J Cardiol Heart Vasc. 2024 Feb;51:101367.

Gasperetti A, Carrick R, Protonotarios A, et al. Long-term arrhythmic follow-up and risk stratification of patients with desmoplakin-associated arrhythmogenic right ventricular cardiomyopathy. JACC Adv. 2024 Feb;3(3):100832.

Gasperetti A, Carrick RT, Protonotarios A, et al. Clinical features and outcomes in carriers of pathogenic desmoplakin variants. Eur Heart J. 2025 Jan;46(4):362-376.

Ghazy T, Elzanaty N, Lackner HK, et al. Prevalence and influence of genetic variants on follow-up results in patients surviving thoracic aortic therapy. J Clin Med. 2024 Sep;13(17):5254.

Gómez J, Reguero JR, Morís C, et al. Mutation analysis of the main hypertrophic cardiomyopathy genes using multiplex amplification and semiconductor next-generation sequencing. Circ J. 2014;78(12):2963-2971.

Gomez-Mayorga JL, Yadavalli SD, Allievi S, et al. National registry insights on genetic aortopathies and thoracic endovascular aortic interventions. J Vasc Surg. 2024 Oct;80(4):1015-1024.e7.

Grebur K, Mester B, Fekete BA, et al. Genetic, clinical and imaging implications of a noncompaction phenotype population with preserved ejection fraction. Front Cardiovasc Med. 2024 Feb;11:1337378.

Gruner C, Ivanov J, Care M, et al. Toronto hypertrophic cardiomyopathy genotype score for prediction of a positive genotype in hypertrophic cardiomyopathy. Circ Cardiovasc Genet. 2013 Feb;6(1):19-26.

Hathaway J, Helio K, Saarinen I, et al. Diagnostic yield of genetic testing in a heterogeneous cohort of 1,376 HCM patients. BMC Cardiovasc Disord. 2021 Mar;21(1):126.

Hayes, Inc. Clinical Utility Evaluation. Genetic testing for family members of individuals with Brugada syndrome. Hayes, Inc.; September 28, 2018d, updated August 1, 2022.

Hayes, Inc. Clinical Utility Evaluation. Genetic testing for family members of individuals with catecholaminergic polymorphic ventricular tachycardia. Hayes, Inc.; December 11, 2018b, updated October 24, 2022.

Hayes, Inc. Clinical Utility Evaluation. Genetic testing for individuals clinically diagnosed with Brugada syndrome. Hayes, Inc.; September 2018c, updated August 1, 2022.

Hayes, Inc. Clinical Utility Evaluation. Genetic testing for individuals clinically diagnosed with catecholaminergic polymorphic ventricular tachycardia. Hayes, Inc.; December 11, 2018a, updated October 24, 2022.

Hayes, Inc. Precision Medicine Research Brief. PrecisionCHD (Cardio Diagnostics Inc.). Hayes, Inc.; April 10, 2024.

Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2022 May;79(17):e263-e421. Erratum in: J Am Coll Cardiol. 2023 Apr;81(15):1551.

Hermida A, Jedraszak G, Ader F, et al. Systematic analysis of *SCN5A* variants associated with inherited cardiac diseases. Heart Rhythm. 2025 Mar;22(3):844-851.

Hershberger RE, Givertz MM, Ho CY, et al. Genetic evaluation of cardiomyopathy: a Heart Failure Society of America practice guideline. J Card Fail. 2018 May;24(5):281-302.

Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. J Am Coll Cardiol. 2010 Apr;55(14):e27-e129. Erratum in: J Am Coll Cardiol. 2013 Sep;62(11):1039-1040.

Hoogendoorn JC, Bosman LP, van der Heijden JF, et al. Different underlying aetiologies in patients presenting with ventricular tachycardia fulfilling task force criteria for arrhythmogenic right ventricular cardiomyopathy: initial suspicion based on the 12-lead electrocardiogram. Europace. 2025 Aug;27(8):euaf136.

Hull LE, Aday AW, Bui QM, et al. Direct-to-consumer genetic testing for cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2025 Apr;151(14):e905-e917.

Ingles J, Sarina T, Yeates L, et al. Clinical predictors of genetic testing outcomes in hypertrophic cardiomyopathy. Genet Med. 2013 Dec;15(12):972-977.

Iribarren C, Lu M, Elosua R, et al. Joint consideration of LDL-C and polygenic risk for coronary heart disease risk assessment. JACC Adv. 2025 Nov;4(11 Pt 1):102228.

Proprietary Information of UnitedHealthcare. Copyright 2026 United HealthCare Services, Inc.

Iribarren C, Lu M, Elosua R, et al. Polygenic risk and incident coronary heart disease in a large multiethnic cohort. Am J Prev Cardiol. 2024a Mar;18:100661.

Iribarren C, Lu M, Gulati M, et al. Interplay between lifestyle factors and polygenic risk for incident coronary heart disease in a large multiethnic cohort. Int J Cardiol Cardiovasc Risk Prev. 2024b Nov;23:200350.

Iribarren C, Lu M, Jorgenson E, et al. Clinical utility of multimarker genetic risk scores for prediction of incident coronary heart disease: a cohort study among over 51,000 individuals of European ancestry. Circ Cardiovasc Genet. 2016 Dec;9(6):531-540. Erratum in: Circ Cardiovasc Genet. 2017 Apr;10(2):e000036.

Iribarren C, Lu M, Jorgenson E, et al. Weighted multi-marker genetic risk scores for incident coronary heart disease among individuals of African, Latino and East-Asian Ancestry. Sci Rep. 2018 May;8(1):6853.

Isselbacher EM, Preventza O, Black JH 3rd, et al. 2022 ACC/AHA guideline for the diagnosis and management of aortic disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation. 2022 Dec;146(24):e334-e482.

Jabbari J, Jabbari R, Nielsen MW, et al. New exome data question the pathogenicity of genetic variants previously associated with catecholaminergic polymorphic ventricular tachycardia. Circ Cardiovasc Genet. 2013 Oct;6(5):481-489.

Joglar JA, Chung MK, Armbruster AL, et al. 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2024 Jan;149(1):e1-e156. Errata in: Circulation. 2024 Jan;149(1):e167.; Circulation. 2024 Feb;149(9):e936.; Circulation. 2024 Jun;149(24):e1413.

Johnson R, Fletcher RA, Peters S, et al. Titin–related familial dilated cardiomyopathy: factors associated with disease onset. Eur Heart J. 2025 Dec;46(48):5240-5257.

Khera AV, Emdin CA, Drake I, et al. Genetic risk, adherence to a healthy lifestyle, and coronary disease. n Engl J Med. 2016 Dec;375(24):2349-2358.

Kukavica D, Trancuccio A, Mazzanti A, et al. Nonmodifiable risk factors predict outcomes in Brugada syndrome. J Am Coll Cardiol. 2024 Nov;84(21):2087-2098.

Landstrom AP, Kim JJ, Gelb BD, et al. Genetic testing for heritable cardiovascular diseases in pediatric patients: a scientific statement from the American Heart Association. Circ Genom Precis Med. 2021 Oct;14(5):e000086.

Laws JL, Shabani M, Williams HL, et al. Genetic evaluation of early-onset atrial fibrillation: impact on patient management. Eur Heart J. 2026 Apr;47(13):1554-1572.

Li L, Pang S, Starnecker F, et al. Integration of a polygenic score into guideline–recommended prediction of cardiovascular disease. Eur Heart J. 2024 May;45(20):1843-1852.

Liu H, Zhang Y, Zhao Y, et al. Research progress and clinical translation potential of coronary atherosclerosis diagnostic markers from a genomic perspective. Genes (Basel). 2025 Jan;16(1):98.

Loar RW, Bos JM, Will ML, et al. Genotype-phenotype correlations of hypertrophic cardiomyopathy when diagnosed in children, adolescents, and young adults. Congenit Heart Dis. 2015 Nov-Dec;10(6):529-536.

Mahlmann A, Rodionov RN, Behrendt CA, et al. Evaluation of the value of histological examination for the prediction of genetic thoracic proximal aortopathies. J Clin Med. 2024 Mar;13(7):1838.

Mazzarotto F, Girolami F, Boschi B, et al. Defining the diagnostic effectiveness of genes for inclusion in panels: the experience of two decades of genetic testing for hypertrophic cardiomyopathy at a single center. Genet Med. 2019 Feb;21(2):284-292.

Mazzarotto F, Tayal U, Buchan RJ, et al. Reevaluating the genetic contribution of monogenic dilated cardiomyopathy. Circulation. 2020 Feb;141(5):387-398.

McBenedict B, Hauwanga WN, Amadi ES, et al. Impact of genetic testing on the diagnosis, management, and prognosis of hypertrophic cardiomyopathy: a systematic review. Cureus. 2024 Oct;16(10):e70993.

Mester B, Lipták Z, Farkas-Sütő KA, et al. Inherited hypertrabeculation? Genetic and clinical insights in blood relatives of genetically affected left ventricular excessive trabeculation patients. Life (Basel). 2025 Jan;15(2):150.

Michels M, Soliman OII, Phefferkorn J, et al. Disease penetrance and risk stratification for sudden cardiac death in asymptomatic hypertrophic cardiomyopathy mutation carriers. Eur Heart J. 2009 Nov;30(21):2593-2598.

Millat G, Chanavat V, Rousson R. Evaluation of a new NGS method based on a custom AmpliSeq library and Ion Torrent PGM sequencing for the fast detection of genetic variations in cardiomyopathies. Clin Chim Acta. 2014 Jun;433:266-271.

Mora-Ayestarán N, Ochoa JP, Gómez-González C, et al. Arrhythmic genotypes in dilated cardiomyopathy and risk of advanced heart failure. Eur Heart J. 2025 Dec;46(48):5222-5233.

Proprietary Information of UnitedHealthcare. Copyright 2026 United HealthCare Services, Inc.

Morgat C, Fressart V, Porretta AP, et al. Genetic characterization of KCNQ1 variants improves risk stratification in type 1 long QT syndrome patients. Europace. 2024 Jun;26(6):euae136.

Morris SA, Flyer JN, Yetman AT, et al. Cardiovascular management of aortopathy in children: a scientific statement from the American Heart Association. Circulation. 2024 Sep;150(11):e228-e254.

Mosley JD, Gupta DK, Tan J, et al. Predictive accuracy of a polygenic risk score compared with a clinical risk score for incident coronary heart disease. JAMA. 2020 Feb;323(7):627-635.

Muller SA, Asatryan B, Gasperetti A, et al. Family screening in relatives at risk for plakophilin-2-associated arrhythmogenic right ventricular cardiomyopathy. Circulation. 2025 Aug;152(5):313-326.

Murphy SL, Anderson JH, Kapplinger JD, et al. Evaluation of the Mayo Clinic phenotype–based genotype predictor score in patients with clinically diagnosed hypertrophic cardiomyopathy. J Cardiovasc Transl Res. 2016 Apr;9(2):153-161.

Musunuru K, Hershberger RE, Day SM, et al. Genetic testing for inherited cardiovascular diseases: a scientific statement from the American Heart Association. Circ Genom Precis Med. 2020 Aug;13(4):e000067.

Myers MC, Wang S, Zhong Y, et al. Prevalence of genetically associated dilated cardiomyopathy: a systematic literature review and meta-analysis. Cardiol Res. 2024 Aug;15(4):233-245.

Naderian M, Hamed ME, Vaseem AA, et al. Effect of disclosing a polygenic risk score for coronary heart disease on adverse cardiovascular events. Circ Genom Precis Med. 2025 Apr;18(2):e004968.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Genetic/familial high-risk assessment: breast, ovarian, pancreatic, and prostate. v3.2025.

Nielsen JC, Lin Y-J, de Oliveira Figueiredo MJ, et al. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) expert consensus on risk assessment in cardiac arrhythmias: use the right tool for the right outcome, in the right population. Heart Rhythm. 2020 Sep;17(9):e269-e316.

Nielsen SK, Hansen FG, Rasmussen TB, et al. Major cardiac events in patients and relatives with hereditary hypertrophic cardiomyopathy. JACC Adv. 2023 Sep;2(8):100604.

Niimura H, Bachinski LL, Sangwatanaroj S, et al. Mutations in the gene for cardiac myosin–binding protein C and late-onset familial hypertrophic cardiomyopathy. n Engl J Med. 1998 Apr;338(18):1248-1257.

Nurmohamed NS, Shim I, Gaillard EL, et al. Polygenic risk is associated with long-term coronary plaque progression and high-risk plaque. JACC Cardiovasc Imaging. 2024 Dec;17(12):1445-1459.

Olivotto I, Girolami F, Ackerman MJ, et al. Myofilament protein gene mutation screening and outcome of patients with hypertrophic cardiomyopathy. Mayo Clin Proc. 2008 Jun;83(6):630-638.

Ommen SR, Ho CY, Asif IM, et al. 2024 AHA/ACC/AMSSM/HRS/PACES/SCMR guideline for the management of hypertrophic cardiomyopathy: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation. 2024 Jun;149(23):e1239-e1311. Erratum in: Circulation. 2024 Aug;150(8):e198.

O'Sullivan JW, Raghavan S, Marquez-Luna C, et al. Polygenic risk scores for cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2022 Aug;146(8):e93-e118.

Pannone L, Bisignani A, Osei R, et al. Genetic testing in Brugada syndrome: a 30-year experience. Circ Arrhythm Electrophysiol. 2024 Apr;17(4):e012374.

Park H, Kim D, You SC, et al. European and US guideline-based statin eligibility, genetically predicted coronary artery disease, and the risk of major coronary events. J Am Heart Assoc. 2024 May;13(9):e032831.

Patel AP, Wang M, Ruan Y, et al. A multi-ancestry polygenic risk score improves risk prediction for coronary artery disease. Nat Med. 2023 Jul;29(7):1793-1803.

Peters S, Thompson BA, Perrin M, et al. Arrhythmic phenotypes are a defining feature of dilated cardiomyopathy-associated *SCN5A* variants: a systematic review. Circ Genom Precis Med. 2022 Feb;15(1):e003432.

Pirruccello JP, Khurshid S, Lin H, et al. The AORTA gene score for detection and risk stratification of ascending aortic dilation. Eur Heart J. 2024 Oct;45(40):4318-4332.

Põld A, Toompere K, Elken A, et al. Evaluating the impact of communicating high polygenic risk for coronary artery disease on the health behaviour of young overweight adults: a pragmatic randomised controlled trial. Sci Rep. 2026 Jan;16(1):4907.

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Rehder C, Bean LJH, Bick D, et al. ACMG Laboratory Quality Assurance Committee: next-generation sequencing for constitutional variants in the clinical laboratory, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021 Aug;23(8):1399-1415.

Restrepo-Cordoba MA, Campuzano O, Ripoll-Vera T, et al. Usefulness of genetic testing in hypertrophic cardiomyopathy: an analysis using real-world data. J Cardiovasc Transl Res. 2017 Feb;10(1):35-46. Erratum in: J Cardiovasc Transl Res. 2019 Aug;12(4):389-390.

Richard P, Charron P, Carrier L, et al. Hypertrophic cardiomyopathy: distribution of disease genes, spectrum of mutations, and implications for a molecular diagnosis strategy. Circulation. 2003 May;107(17):2227-2232. Erratum in: Circulation. 2004 Jun;109(25):3258.

Rubattu S, Bozzao C, Pennacchini E, et al. A next-generation sequencing approach to identify gene mutations in early- and late-onset hypertrophic cardiomyopathy patients of an Italian cohort. Int J Mol Sci. 2016 Jul;17(8):1239.

Schwartz PJ and Crotti L. QTc behavior during exercise and genetic testing for the long-QT syndrome. Circulation. 2011 Nov;124(20):2181-2184.

Seidelmann SB, Smith E, Subrahmanyan L, et al. Application of whole exome sequencing in the clinical diagnosis and management of inherited cardiovascular diseases in adults. Circ Cardiovasc Genet. 2017 Feb;10(1):e001573.

Stroeks SLVM, Wang P, Merlo M, et al. Impact of genotype-phenotype associations on prognosis in dilated cardiomyopathy. Eur J Heart Fail. 2025 Dec;27(12):3205-3218.

Sun L, Pennells L, Kaptoge S, et al. Polygenic risk scores in cardiovascular risk prediction: a cohort study and modelling analyses. PLoS Med. 2021 Jan;18(1):e1003498.

Topriceanu C-C, Pereira AC, Moon JC, et al. Meta-analysis of penetrance and systematic review on transition to disease in genetic hypertrophic cardiomyopathy. Circulation. 2024 Jan;149(2):107-123.

Towbin JA, McKenna WJ, Abrams DJ, et al. 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy: executive summary. Heart Rhythm. 2019 Nov;16(11):e373-e407.

Tuijnenburg F, Proost VM, Thollet A, et al. Long-term prognosis of patients with an *SCN5A* loss-of-function variant and progressive cardiac conduction disorder or Brugada syndrome. Heart Rhythm. 2025 May;22(5):1321-1329.

Van Driest SL, Ellsworth EG, Ommen SR, et al. Prevalence and spectrum of thin filament mutations in an outpatient referral population with hypertrophic cardiomyopathy. Circulation. 2003 Jul;108(4):445-451.

van Waning JI, Caliskan K, Hoedemaekers YM, et al. Genetics, clinical features, and long-term outcome of noncompaction cardiomyopathy. J Am Coll Cardiol. 2018 Feb;71(7):711-722.

van Waning JI, Moesker J, Heijsman D, et al. Systematic review of genotype-phenotype correlations in noncompaction cardiomyopathy. J Am Heart Assoc. 2019 Dec;8(23):e012993.

Virani SS, Newby LK, Arnold SV, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2023 Aug;82(9):833-955. Errata in: J Am Coll Cardiol. 2023 Oct;82(18):1808.; J Am Coll Cardiol. 2024 Apr;83(17):1716.

Watkins H, McKenna WJ, Thierfelder L, et al. Mutations in the genes for cardiac troponin T and alpha-tropomyosin in hypertrophic cardiomyopathy. n Engl J Med. 1995 Apr;332(16):1058-1064.

Weizman O, Gandjbakhch E, Magnin-Poull I, et al. Molecular genetic screening after non-ischaemic sudden cardiac arrest and no overt cardiomyopathy in real life: a major tool for the aetiological diagnostic work-up. Arch Cardiovasc Dis. 2024 Jun-Jul;117(6-7):382-391.

Wilde AAM, Semsarian C, Márquez MF, et al. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) expert consensus statement on the state of genetic testing for cardiac diseases. Heart Rhythm. 2022 Jul;19(7):e1-e60.

Williams MS, Levine GN, Kalra D, et al. 2025 AHA/ACC clinical performance and quality measures for patients with chronic coronary disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Performance Measures. J Am Coll Cardiol. 2025 Jul;85(25):2504-2535.

Yoneda ZT, Anderson KC, Quintana JA, et al. Early-onset atrial fibrillation and the prevalence of rare variants in cardiomyopathy and arrhythmia genes. JAMA Cardiol. 2021 Dec;6(12):1371-1379.

Zou Y, Wang J, Liu X, et al. Multiple gene mutations, not the type of mutation, are the modifier of left ventricle hypertrophy in patients with hypertrophic cardiomyopathy. Mol Biol Rep. 2013 Jun;40(6):3969-3976.

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Policy History/Revision Information

Date	Summary of Changes

09/01/2026	**Related Policies**
	• Removed reference link to the Medical Policy titled:
	  ○ *FDA Cleared or Approved Companion Diagnostic Testing*
	  ○ *Molecular Oncology Testing for Hematologic Cancer Diagnosis, Prognosis, and Treatment Decisions*
	  ○ *Molecular Oncology Testing for Solid Tumor Cancer Diagnosis, Prognosis, and Treatment Decisions*
	  ○ *Pharmacogenetic Panel Testing*
	Coverage Rationale
	• Added instruction to refer to the Medical Policy titled:
	  ○ *Chromosome Microarray Testing (Non-Oncology Conditions)* for chromosome microarray testing related to isolated, severe congenital heart disease
	  ○ *Genetic Testing for Neurological Disorders* for cardiomyopathies that present primarily as neuromuscular disorders
	• Replaced language indicating "pretest genetic counseling is *strongly* recommended *in order* to inform persons being tested about the advantages and limitations of the test as applied to *a* unique *person*" with "pretest genetic counseling is recommended to inform persons being tested about the advantages and limitations of the test as applied to *their* unique *situation*"
	Arrhythmias
	• Replaced language indicating "*multi-gene* panel testing for the diagnosis of a *hereditary* arrhythmia syndrome is proven and medically necessary in individuals with a confirmed or suspected diagnosis of any of the [listed] conditions" with "*Targeted* Panel testing *of five or more genes* for the diagnosis of a *heritable* arrhythmia syndrome is proven and medically necessary in an individual with a confirmed or suspected diagnosis of any of the [listed] conditions"
	• Replaced reference to "*familial* long QT syndrome" with "long QT syndrome"
	Cardiomyopathies
	• Replaced language indicating "*multi-gene* panel testing for the diagnosis of a *hereditary* cardiomyopathy is proven and medically necessary in individuals with a confirmed or suspected diagnosis of any of the [listed] conditions" with "*Targeted* Panel testing *of five or more genes* for the diagnosis of a *heritable* cardiomyopathy is proven and medically necessary in an individual with a confirmed or suspected diagnosis of any of the [listed] conditions"
	• Revised list of proven and medically necessary conditions; replaced "dilated cardiomyopathy, without an identifiable cause, when an individual has cardiac conduction disease *(first-, second-, or third-degree block)*" with "dilated cardiomyopathy, without an identifiable cause, when an individual has cardiac conduction disease, *such as atrioventricular block*"
	Thoracic Aortic Disease
	• Replaced language indicating "*multi-gene* panel testing is proven and medically necessary for either of the [listed conditions]" with "*Targeted* Panel testing *of five or more genes* is proven and medically necessary for either of the [listed conditions]"
	Testing Based Only on Family History
	• Replaced language indicating:
	  ○ "*Multi-gene* panel testing for the diagnosis of *inherited arrhythmic disorders* or cardiomyopathy is proven and medically necessary in asymptomatic individuals who have *one* of the [listed] conditions" with "*Targeted* Panel testing *of five or more genes* for the diagnosis of *a heritable arrhythmia syndrome* or cardiomyopathy is proven and medically necessary in asymptomatic individuals who have *either* of the [listed] conditions"
	  ○ "All other genetic testing for cardiomyopathies, arrhythmias, or aortic vascular disease [not listed in the policy as proven and medically necessary] is unproven and not medically necessary due to insufficient evidence of efficacy *(this does not apply to chromosome microarray analysis for isolated severe congenital heart disease)*" with "all other genetic testing for cardiomyopathies, arrhythmias, or aortic vascular disease [not listed in the policy as proven and medically necessary] is unproven and not medically necessary due to insufficient evidence of efficacy"
	• Replaced reference to "*congenital* long QT syndrome (LQTS)" with "long QT syndrome (LQTS)"

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Date	Summary of Changes

	• Added language to indicate Comprehensive Panel tests that are intended to evaluate multiple genes associated with multiple categories of clinically distinct cardiomyopathies, arrhythmias, and/or aortic vascular disorders are unproven and not medically necessary due to insufficient evidence of efficacy
	Coronary Artery Disease
	• Added language to clarify genetic testing for coronary artery disease *risk* is unproven and not medically necessary
	• Revised list of unproven and not medically necessary indications; replaced "microarray or other genetic profiles *for cardiac disease risk (e.g., Cardiac DNA Insight®, Cardiac Healthy Weight DNA Insight®, Cardio IQ® gene tests and panels)*" with "microarray, *polygenic risk scores*, or other genetic profiles *such as Allelica PRS, CARDIO inCode-Score, Epi+Gen CHD, or PrecisionCHD*"
	Definitions
	• Added definition of:
	  ○ Comprehensive Panel
	  ○ Targeted Panel
	• Removed definition of "Multi-Gene Panel"
	Applicable Codes
	• Added HCPCS code S3865
	Supporting Information
	• Updated *Description of Services*, *Clinical Evidence*, and *References* sections to reflect the most current information
	• Archived previous policy version 2026T0552CC

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its policies and guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

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