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CONTEMPORARY REVIEW

What Should a Clinical Cardiologist Know About Cardiogenetics?

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ABSTRACT: Inherited cardiovascular diseases are becoming increasingly prominent in clinical practice, significantly impacting diagnosis, risk assessment, and family screening strategies. Progress in genetic testing has broadened access to cardiogenetic evaluations, while also presenting new challenges in interpreting variants and incorporating findings into clinical care. This narrative review explores 20 essential questions that clinical cardiologists may face when dealing with suspected or confirmed inherited cardiac conditions. Organized as a practical, question-driven guide, it outlines when to consider a genetic cause, how to choose and interpret genetic tests, and how to manage patients regardless of their genetic test results. The review emphasizes variant classification based on American College of Medical Genetics and Genomics criteria, the importance of clinical context in interpreting uncertain results, and the principles behind family cascade screening. Particular attention is given to the management of relatives who carry a genetic variant but show no symptoms, and to the current limitations of genetic testing technologies (eg, performance). Ethical considerations, including the appropriate timing of testing in children minors, are also discussed. By connecting genetic insights with clinical cardiology, this review aims to support practical, informed decision making and promote effective collaboration with cardiogenetic specialists.

Key Words: cardiogenetics ■ cardiomyopathies ■ cascade screening ■ channelopathies ■ genetic testing

Over the past 2 decades, the integration of genetics into cardiovascular medicine has shifted from a niche interest to a clinical necessity.[1] Advances in molecular diagnostics and the growing availability of next-generation sequencing have significantly improved our ability to identify the genetic basis of many inherited cardiac conditions, particularly cardiomyopathies and channelopathies.[2,3] Increasing evidence has highlighted the role of genetics not only in diagnosis but also in prognosis.[4] For example, in dilated cardiomyopathy (DCM), variants on specific genes are associated with a higher risk of arrhythmias, disease progression, and adverse outcomes, directly impacting risk stratification and management strategies.[5]

Despite these advances, many clinical cardiologists still perceive cardiogenetics as a highly specialized and complex field that remains largely disconnected from routine clinical practice. However, the timely recognition of red flags, appropriate use of genetic testing, and effective integration of genetic results into clinical decision making can significantly influence diagnosis, prognosis, therapeutic choices, and family screening.[6]

Effective collaboration and communication between clinical cardiologists and "cardiogeneticists" (cardiologists with specific expertise in inherited heart disease) are becoming increasingly essential to ensure optimal care for patients with suspected genetic cardiac disease. Such collaboration also helps determine which

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Nonstandard Abbreviations and Acronyms

ARVC	arrhythmogenic right ventricular cardiomyopathy
CPVT	catecholaminergic polymorphic ventricular tachycardia
DCM	dilated cardiomyopathy
HCM	hypertrophic cardiomyopathy
SCD	sudden cardiac death
VUS	variant of uncertain significance

patients require referral to a dedicated, specialized center and which can be managed within general cardiology settings with appropriate guidance. Specialized cardiogenetic centers should ideally offer a comprehensive, multidisciplinary care model, including the involvement of a medical geneticist, cardiogeneticist, cardiac imaging specialist, heart failure specialist, electrophysiologist, cardiac surgeon, sports cardiologist, anatomopathologist, psychologist, and dedicated nursing staff, such as a familial or case manager.[7] This team-based approach ensures accurate diagnosis, risk stratification, personalized surveillance, and coordinated care across affected families.[8]

This article aims to provide practical guidance for cardiologists who are not specialized in genetics but wish to understand when and how to consider a genetic basis in their patients and to better support their subsequent referral and management within specialized care pathways. Through 20 concise and focused questions, we address the essential knowledge and practical steps needed to recognize, investigate, and manage inherited cardiovascular disease in everyday clinical practice. Our goal is to bridge the gap between cardiogenetics and general cardiology, empowering clinicians to confidently navigate genetic concepts, collaborate effectively within multidisciplinary teams, and ultimately provide more precise, personalized care to their patients.

Before delving into the clinical questions, we provide a glossary of key cardiogenetic terms commonly encountered in reports and clinical consultations (Table S1).

WHY SHOULD CLINICAL CARDIOLOGISTS CARE ABOUT CARDIOGENETICS TODAY?

Cardiogenetics has become a cornerstone of modern cardiovascular care.[9] While once considered a hyperspecialized field relevant only to rare inherited disorders, today genetic evaluation plays a critical role in routine cardiology practice. This shift is driven by growing evidence that genetic information can meaningfully influence diagnosis, clinical management, risk stratification, and family-based preventive strategies.[10] Cardiologists are frequently the first specialists to encounter patients with conditions that may have a genetic basis, such as cardiomyopathy, unexplained arrhythmias, sudden cardiac death (SCD) in the family, or early-onset heart failure. As such, they are uniquely positioned to recognize "red flags," initiate appropriate referrals, and facilitate genetic testing when indicated.[11] Moreover, understanding the genetic framework of a patient's disease allows cardiologists to personalize care by adapting surveillance intervals, tailoring treatment decisions (eg, timing of implantable cardioverter-defibrillator [ICD] implantation), and determining eligibility for family screening.[12] Nonetheless, a recent survey underscored the high variability among cardiologists in their perceptions and practices of cardiogenetic testing, with only a minority feeling confident in independently ordering or interpreting results. This heterogeneity further underscores the importance of standardizing cardiogenetic approaches in general cardiology.[13]

Professional cardiological societies have progressively acknowledged this evolution: the 2020 American Heart Association/American College of Cardiology Guidelines on Genetic Testing for Inherited Cardiovascular Diseases,[14] the 2022 European Society of Cardiology Position Paper on Genetic Testing[15] and the 2023 European Society of Cardiology Guidelines on Cardiomyopathies[5] strongly encourage cardiologists to integrate genetic assessment into the clinical workflow when a hereditary disease is suspected.

WHICH CARDIOVASCULAR DISEASES HAVE A WELL-DEFINED GENETIC BASIS?

Several cardiovascular conditions have a well-established genetic origin, particularly those involving the myocardium,[16] cardiac conduction system,[17] or conditions predisposing to SCD.[18] These disorders are often monogenic and inherited through an autosomal dominant pattern, although variable expressivity and incomplete penetrance are common.[19] These 2 phenomena (defined in the Table S1 Glossary) represent major clinical challenges, as they may obscure diagnosis, complicate risk stratification, and influence decisions regarding cascade testing and the management of family members.

Cardiomyopathies

1. Hypertrophic cardiomyopathy (HCM): Most frequently associated with actionable variants in sarcomeric genes such as *MYBPC3*, *MYH7, TNNT2*,

and *TNNI3*.[20] It is the most common inherited cardiomyopathy, with autosomal dominant inheritance and age-dependent penetrance.[21] A number of HCM phenocopies, namely, systemic diseases with cardiac involvement mimicking HCM, must be included in the differential diagnosis. These include transthyretin hereditary amyloidosis,[22] Danon disease,[23] Fabry disease,[24] mitochondrial cytopathies, and neuromuscular disorders such as muscular dystrophies (Duchenne muscular dystrophy, Emery–Dreifuss muscular dystrophy), Friedreich ataxia, and myotonic dystrophy.[25]

2. DCM: A genetically heterogeneous and often elusive condition, involving genes such as *TTN*, *LMNA*, *FLNC*, and *RBM20*, among others. A genetic origin is more likely in the presence of conduction disease, arrhythmias, myopathy, or a family history. Beyond monogenic causes, polygenic inheritance also contributes, with modifiers and triggers such as alcohol abuse, chemotherapy, and myocarditis playing an important role.[26]
3. Arrhythmogenic right ventricular cardiomyopathy (ARVC): Often due to variants in desmosomal genes like *PKP2, DSP, DSG2, DSC2*, and *JUP*. Left-dominant forms and biventricular presentations are increasingly recognized, including those associated with nondesmosomal genes (*PLN*, *TMEM43*, and *DES*). Importantly, ARVC is often characterized by incomplete penetrance and variable expressivity, and accumulating evidence suggests that exercise may accelerate disease onset and progression in genetically predisposed individuals, highlighting the potential role of lifestyle counseling in management.[27]
4. Nondilated left ventricular cardiomyopathy: Newly recognized phenotype characterized by structural or functional abnormalities of the left ventricle without chamber dilatation.[5] Often underdiagnosed an undertested, it may harbor actionable variants in genes shared by DCM and ARVC.[28]
5. Restrictive cardiomyopathy: Rare clinical entity, often overlapping with sarcomeric or storage diseases, and may be genetically determined. It should be distinguished from cardiomyopathy with restrictive physiology, as in restrictive cardiomyopathy the restrictive pattern is not secondary to morphological changes (eg, increased wall thickness).[29]

Channelopathies

1. Long QT syndrome: Caused by variants in cardiac ion channel genes such as *KCNQ1*, *KCNH2*, and *SCN5A*. Genotype influences both risk and therapeutic choices.[30]
2. Brugada syndrome: Most commonly associated with *SCN5A* variants, although many cases remain genetically elusive.[31]
3. Catecholaminergic polymorphic ventricular tachycardia (CPVT): Typically linked to *RYR2* mutations; high arrhythmic risk during adrenergic stress.[32]
4. Short QT syndrome and idiopathic ventricular fibrillation: Rare, genetically heterogeneous, and challenging to diagnose definitively.[15]

Inherited Arrhythmia and Conduction Disorders

1. Progressive cardiac conduction disease at a young age: Can be a manifestation of mutations in *LMNA*, *SCN5A*, *EMD*, or *NKX2-5*. Particularly relevant when associated with DCM or ventricular arrhythmias.[33]
2. Early-onset atrial fibrillation (<60 years): Increasingly recognized as a potentially genetic entity, especially when associated with familial aggregation or absence of structural heart disease. Variants in *TTN*, *NKX2-5*, or *KCNQ1* may be implicated.[34]

Other Inherited Conditions

1. Familial hypercholesterolemia: Due to mutations in *LDLR*, *APOB*, or *PCSK9*, leading to premature atherosclerosis. Early diagnosis is critical for cardiovascular prevention.[35]
2. Inherited aortopathies: Such as Marfan syndrome (*FBN1*), Loeys–Dietz syndrome (*TGFBR1/2*, *SMAD3*), and nonsyndromic familial thoracic aortic aneurysm (eg, *ACTA2* mutations), as well as vascular Ehlers–Danlos syndrome (*COL3A1*) and aortic involvement in DiGeorge syndrome.[36]
3. Heritable pulmonary arterial hypertension: Most commonly associated with mutations in *BMPR2*, but also in *ACVRL1*, *ENG*, and *SMAD9*. It is a rare condition characterized by dysregulated pulmonary vascular cell proliferation, impaired apoptosis, and progressive vascular remodeling.[37]
4. Inherited inflammatory pericardial diseases: Genetic predisposition has been reported in recurrent or refractory pericarditis, often linked to monogenic autoinflammatory syndromes such as familial Mediterranean fever or tumor necrosis factor receptor–associated periodic syndrome.[38]

WHAT IS THE DIFFERENCE BETWEEN MONOGENIC, OLIGOGENIC, AND POLYGENIC INHERITANCE?

Understanding the different patterns of genetic inheritance is essential for interpreting genetic test results and anticipating the clinical variability seen in inherited cardiovascular diseases. The 3 main categories—monogenic, oligogenic, and polygenic—represent distinct models of how genetic variants contribute to disease.[39]

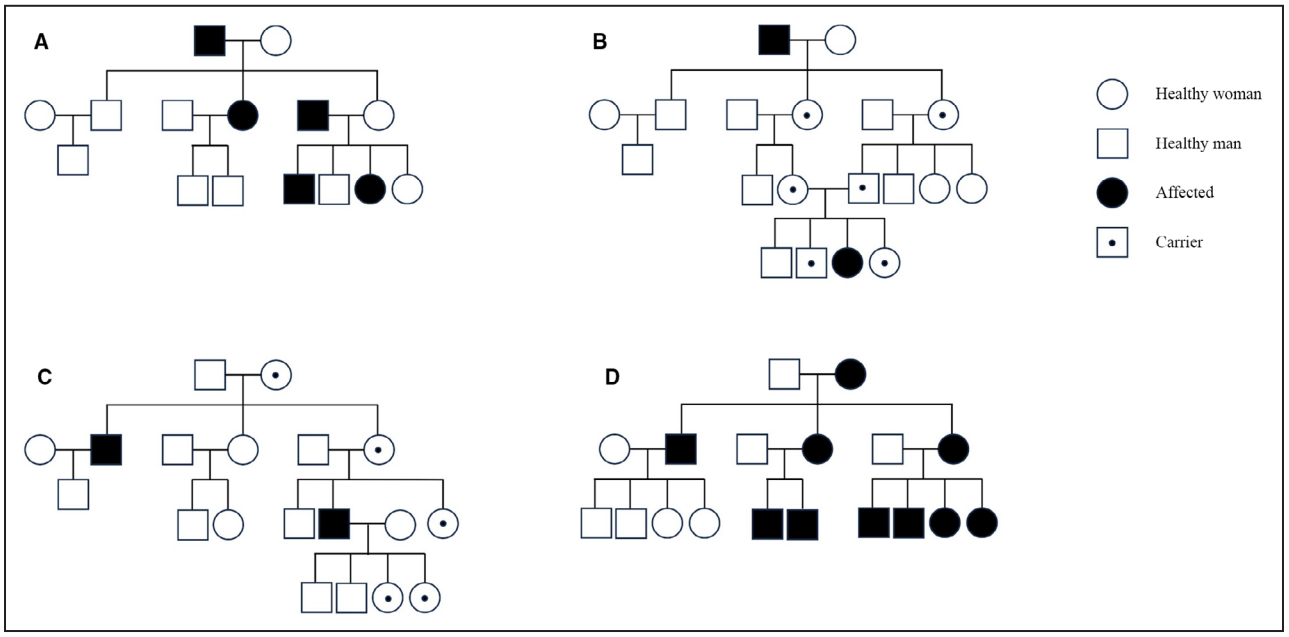

Figure 1. Different patterns of inheritance.
A, Autosomal dominant; (**B**) autosomal recessive; (**C**) X-linked recessive; (**D**) mitochondrial.

Monogenic Inheritance

In monogenic (or Mendelian) disorders, a single actionable variant in 1 gene is sufficient to cause disease. These conditions typically follow recognizable inheritance patterns—autosomal dominant, autosomal recessive, X-linked, or mithocondrial—and are the main focus of clinical genetic testing (Figure 1). Monogenic diseases often display variable penetrance and expressivity, meaning not all carriers are symptomatic, and clinical severity/phenotype can differ within the same family.[40,41]

Oligogenic Inheritance

Oligogenic inheritance involves the contribution of ≥2 actionable variants, often in different genes, that together modulate the phenotype. In this model, a primary variant may not be sufficient alone to cause disease but interacts with additional variants to influence expression, severity, or age of onset.[42] This mechanism is increasingly recognized in arrhythmic diseases and atypical cardiomyopathy presentations.[43] Although not routinely evaluated in clinical reports, oligogenic contributions may explain part of the so-called "incomplete penetrance" of known monogenic disorders.[44]

Polygenic Inheritance

In polygenic conditions, disease risk results from the cumulative effect of many common variants (single-nucleotide polymorphisms, population frequency >1%), each contributing a small increase in risk.[45] No single variant causes the disease, but together they can shift an individual's genetic susceptibility above or below the population average.[46] Polygenic inheritance is typical of complex multifactorial conditions such as coronary artery disease,[47] essential hypertension,[48] atrial fibrillation,[49] and hypertriglyceridemia.[50] While polygenic risk scores are not yet part of routine cardiology practice, research suggests that they may soon help stratify risk in individuals with family history but no detectable monogenic mutation, for example, in "mutation-negative" HCM cases.[51]

In clinical practice, monogenic diseases remain the primary target of genetic testing, but the concepts of oligogenic and polygenic inheritance are increasingly important to explain borderline phenotypes, incomplete penetrance, or unexpected disease severity.

WHAT IS THE DIAGNOSTIC YIELD OF GENETIC TESTING IN CARDIOVASCULAR DISEASE?

Inherited cardiomyopathies and channelopathies are more frequent than often assumed, and their recognition is increasing due to broader genetic testing and growing awareness among clinicians.[52] Although many of these conditions were once considered rare, several now fall within the spectrum of "not uncommon" in daily cardiology practice.

Table 1 summarizes the estimated prevalence and corresponding diagnostic yield of genetic testing

Table 1. Estimated Prevalence and Diagnostic Yield of Genetic Testing Across Cardiovascular Diseases

Disease	Estimated prevalence	Genetic testing diagnostic yield	Main genes
Cardiomyopathies			
Hypertrophic cardiomyopathy[53]	1:500	40%–60%	*MYBPC3, MYH7, TNNT2, TNNI3*
Dilated cardiomyopathy[54]	1:250–1:500	20%–40%	*TTN, LMNA, FLNC, RBM20, TMEM43*
Arrhythmogenic right ventricular cardiomyopathy[52]	1:2000–1:5000	60%–70%	*PKP2, DSP, DSG2, DSC2, JUP*
Restrictive cardiomyopathy[5]	Rare	Unknown	*TNNI3, DES, FLNC*
Nondilated left ventricular cardiomyopathy[5]	Unknown	Unknown	*LMNA, DSP, FLNC*
Channelopathies/conduction disorders			
Long QT syndrome[55]	1:2000–2500	70%–80%	*KCNQ1, KCNH2, SCN5A*
Brugada syndrome[30]	1:2000–5000	15%–30%	*SCN5A*
Catecholaminergic polymorphic ventricular tachycardia[31]	<1:10000	≈60%	*RYR2, CASQ2*
Early-onset atrial fibrillation (aged <60 y)[14]	≈1%–2% of population	10%–15%	Polygenic—*TTN, LMNA, SCN5A*
Early-onset conduction disease (aged <50 y)[14]	Unknown	20%–30% in selected cases	*Polygenic—TTN, LMNA, SCN5A*
Aortopathies			
Marfan syndrome[35]	1:5000	≈90%	*FBN1*
Loeys–Dietz syndrome[35]	1:100000	>90%	*GFBR1, TGFBR2, SMAD3, TGFB2*
Vascular Ehlers–Danlos syndrome[35]	1:50000–200000	≈95%	*COL3A1, COL1A1*
Familial thoracic aortic aneurysm[35]	20% considered sporadic TAAD	20%–30%	*ACTA2, MYH11, MYLK, PRKG1*
Dyslipidemias			
Heterozygous familial hypercholesterolemia[34]	1:200–250	60%–80%	*LDLR, APOB, PCSK9*
Homozygous familial hypercholesterolemia[34]	1:160000–1:300000	≈95%	*LDLR, APOB, PCSK9*
Familial combined hyperlipidemia/severe hypertriglyceridemia[34]	1:50–1:600	Low; often polygenic	*APOA5, LPL, APOC2, GPIHBP1*
Others			
Heritable pulmonary arterial hypertension[37]	<1:1000000	≈70%–80%	*BMPR2, ACVRL1, ENG, SMAD9*
Inherited inflammatory pericardial diseases[38]	1:10000	≈15% of recurrent cases	*MEFV, TNFRSF1A, IFIH1, NOD2, NFKBIA*

TAAD indicates thoracic aortic aneurysms and dissections.

(actionable variants) across the spectrum of cardiovascular diseases.[2,53] Among cardiomyopathies, the highest yield of actionable variants is observed in ARVC,[54] exceeding 60%. It remains substantial in HCM,[55] at ≈40% to 60%, and lower in DCM, ranging from 20% to 40%.[56] In contrast, the proper diagnostic yield in nondilated left ventricular cardiomyopathy and restrictive cardiomyopathy is still not well defined.[5] In channelopathies, the rate of actionable variant detection is particularly high in long QT syndrome and CPVT, often exceeding 60%, whereas it is significantly lower in Brugada syndrome, ranging between 15% and 30%.[15,57]

HOW CAN FAMILY HISTORY HELP IDENTIFY INHERITED CARDIOVASCULAR CONDITIONS?

Family history is a fundamental tool in the identification of inherited cardiovascular disease. Despite advances in genetic testing, a carefully collected 3-generation pedigree provides the first and most accessible clue to a heritable condition and remains essential even after genetic results are available.[58]

Key Elements to Explore in Family History

1. Cardiomyopathies, especially when there are multiple affected relatives, early-onset presentation, or "idiopathic" cases without clear secondary causes. In practical terms, it may be helpful to ask whether any relatives have ever been diagnosed with an "enlarged" or "thickened heart."
2. SCD, particularly before the age of 50, or unexplained deaths, drowning, or accidents.
3. Recurrent syncope or arrhythmias, including inherited arrhythmic syndromes.
4. Early-onset atrial fibrillation, pacemaker/ICD implantation, or progressive conduction system disease in young individuals.

5. Premature atherosclerotic cardiovascular disease, such as myocardial infarction or stroke before age 55 in men or 65 in women, raising suspicion for familial hypercholesterolemia.
6. Aortic dissection or aneurysm, especially when occurring at a young age or affecting multiple family members.
7. Cardiac transplantation or end-stage heart failure, especially when occurring in young individuals, affecting multiple family members and in the absence of a clear non-heritable clinical context (eg, ischemic pathogenesis).
8. Early-onset neurosensory or neuromuscular disease or the presence of a syndromic pattern affecting multiple organ systems across family members.

A positive family history significantly increases the pretest probability of an underlying genetic condition and may influence both the decision to perform genetic testing and the interpretation of results, particularly when a variant of uncertain significance (VUS) is identified. Unsurprisingly, clinical prediction models developed to estimate the likelihood of identifying an actionable variant, such as the Madrid DCM Score[59] or the Mayo,[60] Toronto,[61] and machine-learning HCM scores,[62] consistently include family history as a core variable. In these tools, it serves as a powerful modifier of genetic risk and supports appropriate referral, testing, and counseling strategies.

WHICH RED FLAGS MAY INDICATE A POTENTIAL GENETIC PATHOGENESIS?

Adopting a "cardiogenetic mind set" to identify patients with potential genetic cardiovascular disease starts with recognizing red flags: clinical features, ECG findings, or imaging characteristics that raise suspicion for an inherited pathogenesis (Table 2).[63–69] While no single feature is diagnostic, their combination significantly increases the likelihood of an underlying genetic disorder and should prompt further evaluation or referral. ECG abnormalities, arrhythmic burden, and imaging findings often precede or exceed structural disease and can signal a genetic pathogenesis even in asymptomatic patients.[70,71] Together, they provide a noninvasive triad of suspicion, guiding timely referral and increasing the diagnostic yield of genetic testing.

Table 2. Clinical, Electrocardiographic, and Imaging "Red Flags" Suspicious for an Inherited Pathogenesis

Category	Red flags
Clinical	Early onset of disease (aged <50 y)
	Unexplained syncope, cardiac arrest, or SCD
	Events occurring during intense exercise, rest or sleep, emotional stress, or acoustic stimuli
	Family history of cardiomyopathy, arrhythmia, SCD, ICD/pacemaker, or heart failure (see question 5)
	Multisystemic involvement (neuromuscular, skeletal, cognitive, sensorineural, skin)
	Early-onset atrial fibrillation, conduction disease, or nonischemic heart transplant
	Severe phenotype disproportionate to hemodynamic burden
	Recurrent/disproportionate myocarditis or persistent biomarkers despite symptoms resolution
	Recurrent pericarditis with an inflammatory phenotype, refractory to conventional treatment
	Arcus cornealis (aged <45 y), tendon xanthoma, elevated Dutch lipid score
ECG	Low QRS voltages in limb leads
	Pathological Q waves without infarction
	T-wave inversions in right precordial/inferolateral leads
	Prolonged/shortened QT interval or high QT variability
	Brugada pattern (type 1 or dynamic ST elevation in V1–V3)
	Early repolarization or inferolateral J waves
	ε waves or fragmented QRS
	Frequent PVCs, NSVT, or sustained VT
	PR shortening, atrioventricular block, or δ waves with arrhythmias
Imaging	Left ventricular hypertrophy >15 mm and reverse septal morphology, without afterload mismatch
	Unexplained left ventricular systolic dysfunction with preserved dimensions
	Nonischemic regional wall motion abnormalities and/or apical aneurysms
	Right ventricular enlargement/hypertrophy or dysfunction without pulmonary disease
	Extensive late gadolinium enhancement in midwall/subepicardial/patchy/ringlike pattern
	Abnormal interstitial or edema markers (T1/T2 mapping)
	Mitral valve and papillary muscles abnormalities, myocardial crypts, and/or significant hypertrabeculation
	Aortic root dilation at young age and/or with syndromic features/family history
	Unexplained pulmonary hypertension

ICD indicates implantable cardioverter-defibrillator; NSVT, nonsustained ventricular tachycardia; PVCs, premature ventricular contractions; and SCD, sudden cardiac death.

WHO SHOULD BE TESTED FIRST IN THE FAMILY?

The first person to undergo genetic testing in a family is known as the proband, and selecting the most appropriate individual is critical to maximizing both the diagnostic yield and the clinical utility of the test.[72] Whenever possible, testing should begin with the

family member who presents the most severe or well-characterized phenotype. This may include:

1. The individual with the earliest onset of disease;
2. The person with the broadest or most complex phenotype (eg, cardiomyopathy plus arrhythmias);
3. The only clinically affected relative for whom medical data and samples are available;
4. A deceased family member, if postmortem DNA (eg, stored blood or tissue) is accessible;
5. In cases of SCD, a molecular autopsy may be considered when no prior phenotype was documented.

Testing mildly affected or phenotype-negative relatives can result in inconclusive or misleading findings, particularly if a VUS is identified without linkage to a known disease pattern in the family.[73]

WHEN SHOULD THE PATIENT BE REFERRED FOR GENETIC TESTING?

Genetic testing should be considered when there is clinical suspicion of an inherited cardiovascular disease and when the result has the potential to guide diagnosis, prognosis, management, family screening, or reproductive planning.[14,15,74] Referral should ideally occur early in the disease course, before irreversible complications arise and while at-risk family members can still benefit from surveillance or preventive measures.

When to Refer a Patient for Genetic Testing

1. When the result may inform preventive strategies in living first-degree relatives or offspring, through cascade genetic testing and early phenotype surveillance.
2. When the result may support or clarify the diagnosis, for example, in patients with left ventricular hypertrophy, to distinguish sarcomeric HCM from phenocopies (eg, athlete's heart, Fabry disease, amyloidosis, protein kinase AMP–activated noncatalytic subunit γ 2 syndrome).[75]
3. When the result may provide prognostic information and guide clinical decisions. For example, in patients with DCM and left ventricular ejection fraction >35%, a genotype-positive result may support ICD implantation regardless of left ventricular ejection fraction cutoffs.[5]
4. When the result has reproductive implications, such as guiding preconception counseling, prenatal diagnostics, or access to assisted reproductive options like preimplantation genetic testing.[76]

When Not to Refer (or When to Defer Testing)

1. When there is no defined phenotype or family history, and the clinical utility is low, such as when the test result would not change diagnosis, management, or prognosis. For example, genetic testing may be considered clinically futile in older, asymptomatic first-degree relatives without offspring.
2. When the patient has not yet undergone a complete clinical evaluation; testing should always follow structured and deep phenotyping to avoid misinterpretation.
3. When other family members are being considered for testing but the proband has not yet been tested; in such cases, testing the proband first is essential.
4. First-degree relatives of a genotype-negative individual (in whom no actionable variant was found) do not require cascade testing, as they cannot inherit a nonexistent familial variant. This does not exclude the rare possibility of an independent de novo variant in other family members.[77]

Beyond the clinical indications, it is important to recognize that patients may face barriers that hinder genetic testing, ranging from practical limitations (eg, financial or logistic, depending on the health care system) to emotional concerns such as fear, anxiety, or misconceptions about the implications of testing. These issues should be explored openly by the health care team, with clear information provided to patients and guidance through a shared decision-making process, while offering support that is realistic within the available resources of each clinical setting. More broadly, integration of cardiogenetics into clinical practice is also limited by workforce shortages, costs, and access to genetic counseling. At the same time, ethical, legal, and psychosocial aspects, such as insurance concerns, emotional burden, and the implications of cascade testing, must also be addressed to ensure responsible use of genetic information.

HOW IS A GENETIC TEST ACTUALLY PERFORMED?

From the patient's perspective, genetic testing is a simple and nearly noninvasive procedure. However, it involves a complex laboratory workflow and requires thoughtful coordination between the clinical and molecular teams. Understanding how testing is performed helps clinicians appropriately counsel patients and ensure proper preanalytical procedures.

Sample Collection

Genetic testing requires a source of high-quality DNA, which can be obtained through various means:

1. Peripheral blood sample in EDTA tube is the standard and preferred method in most settings. It yields high-quality DNA suitable for all types of genomic analysis.
2. Buccal swab (saliva or cheek epithelial cells) is a valid alternative, especially in children or when phlebotomy is impractical. However, DNA quality and quantity may be inferior, particularly in older or uncooperative patients.
3. Fasting is not required, and no specific time of day is recommended for sample collection.

In all cases, samples are sent to a certified genetic testing laboratory, accompanied by a detailed clinical summary, including phenotype, family pedigree, and diagnostic suspicion. This contextual information is essential for genetic test selection and for accurate variant interpretation.

Molecular Autopsy

Molecular autopsy, also referred to as postmortem genetic testing, consists of genetic analyses performed after SCD to identify an underlying heritable cause.[78] It is particularly relevant in young individuals or when clinical autopsy findings are absent or inconclusive, especially in cases of structurally normal hearts suggesting a channelopathy or concealed cardiomyopathy.[79–82] For this purpose, high-quality DNA can be extracted from stored EDTA blood, frozen tissue samples (eg, spleen, liver), or formalin-fixed paraffin-embedded material.

Molecular autopsy is crucial not only to clarify the cause of death but also to enable cascade testing and risk stratification in surviving family members.[83]

WHAT TYPES OF GENETIC TESTS ARE ADOPTED IN CARDIOGENETICS?

Several types of genetic tests are currently available, differing in scope, resolution, cost, and clinical indication (Table S2). Selecting the appropriate test depends on the patient's phenotype, family history, and the level of clinical suspicion for a monogenic condition.

In summary, most cardiogenetic indications are currently addressed through next-generation sequencing–based gene panels or virtual panels filtered from exome data.[84] Gene selection should follow disease-specific guidelines and is typically based on the patient's phenotype, age at onset, inheritance pattern, and red flags such as conduction disease, syndromic features, or extracardiac involvement.[85] Whenever possible, expert-curated panels (eg, ClinGen-approved gene lists) should be prioritized to avoid inclusion of genes with low or disputed clinical validity.[15,86–88] Cascade family screening is performed by targeted Sanger sequencing of the known familial variant. Finally, broader approaches such as whole exome sequencing, whole genome sequencing, or copy number variation analysis may be useful in complex, syndromic, or unsolved cases but require careful pretest counseling, and expert interpretation, particularly when VUS or incidental findings are encountered.[89–91]

Turnaround time varies with test type, urgency, and laboratory workflow. On average, most cardiovascular genetic tests require several weeks (>4), though some cases may take longer. Clinicians should inform patients that delays may occur, especially in the case of complex bioinformatic interpretation, VUS, decision for family-based segregation analysis.

WHAT ARE THE POSSIBLE RESULTS OF A GENETIC TEST?

Genetic test results are classified according to the American College of Medical Genetics and Genomics guidelines, which provide a standardized framework for variant interpretation.[74] This classification determines the clinical actionability of each result and informs management decisions for both the proband and at-risk relatives.

Five American College of Medical Genetics and Genomics Variant Classes

1. Pathogenic (class 5): Strong and consistent evidence of disease causality; clinically actionable.
2. Likely pathogenic (class 4): High likelihood of pathogenicity (>90%); clinically actionable.
3. VUS (class 3): Conflicting or insufficient evidence regarding pathogenicity. It cannot be used to confirm or exclude a diagnosis; therefore it should not guide treatment or cascade testing.
4. Likely benign (class 2): Strong evidence against pathogenicity (>90% confidence). No clinical action required; often not reported in curated panels.
5. Benign (class 1): Clearly not associated with disease. Common population variants; no clinical relevance.

Once a pathogenic (class 5) or likely pathogenic (class 4) variant is identified in the proband, cascade genetic testing should be extended to first-degree relatives. These variants are considered actionable, meaning that surveillance or preventive measures are warranted even in asymptomatic carriers.

Cascade genetic testing (see Figure 2) enables:

1. Identification of genotype-positive relatives, who benefit from early and targeted phenotyping. These individuals are subclassified as:

- Genotype-positive/phenotype-positive (clinically affected by overt disease).

- Genotype-positive/phenotype-negative (presymptomatic carriers), who remain at risk depending on age, penetrance, and modifier factors.

2. Exclusion of genotype-negative relatives, who can be reassured and discharged from clinical follow-up, avoiding unnecessary anxiety or surveillance.[92,93]

In contrast, when the test in the proband is negative, genetic testing is not indicated in first-degree relatives, as there is no familial variant to test for.[15] In such scenarios, structured, disease-specific phenotypic screening becomes essential, both at baseline and over time. While in this scenario the likelihood of heritability is lower, the absence of a detectable actionable variant in the proband does not exclude a heritable disease mechanism, which may follow a non-Mendelian or polygenic inheritance pattern.[94]

WHAT IS A VUS AND HOW SHOULD IT BE MANAGED CLINICALLY?

A VUS is a genetic finding for which the current evidence is insufficient or conflicting to classify it as clearly pathogenic or benign (class 3, American College of Medical Genetics and Genomics).[74] VUS results are frequent in cardiovascular genetics, especially when dealing with rare variants, less-characterized genes, or patients with mild or atypical phenotypes.[95] Importantly, a VUS should not be used routinely to confirm a diagnosis or guide clinical decisions, including device implantation or cascade testing. The best course of action is phenotype-driven care, periodical reevaluation over time, and multidisciplinary coordination, especially in cases where the gene and family history suggest a high pretest probability of disease. Interpretation of

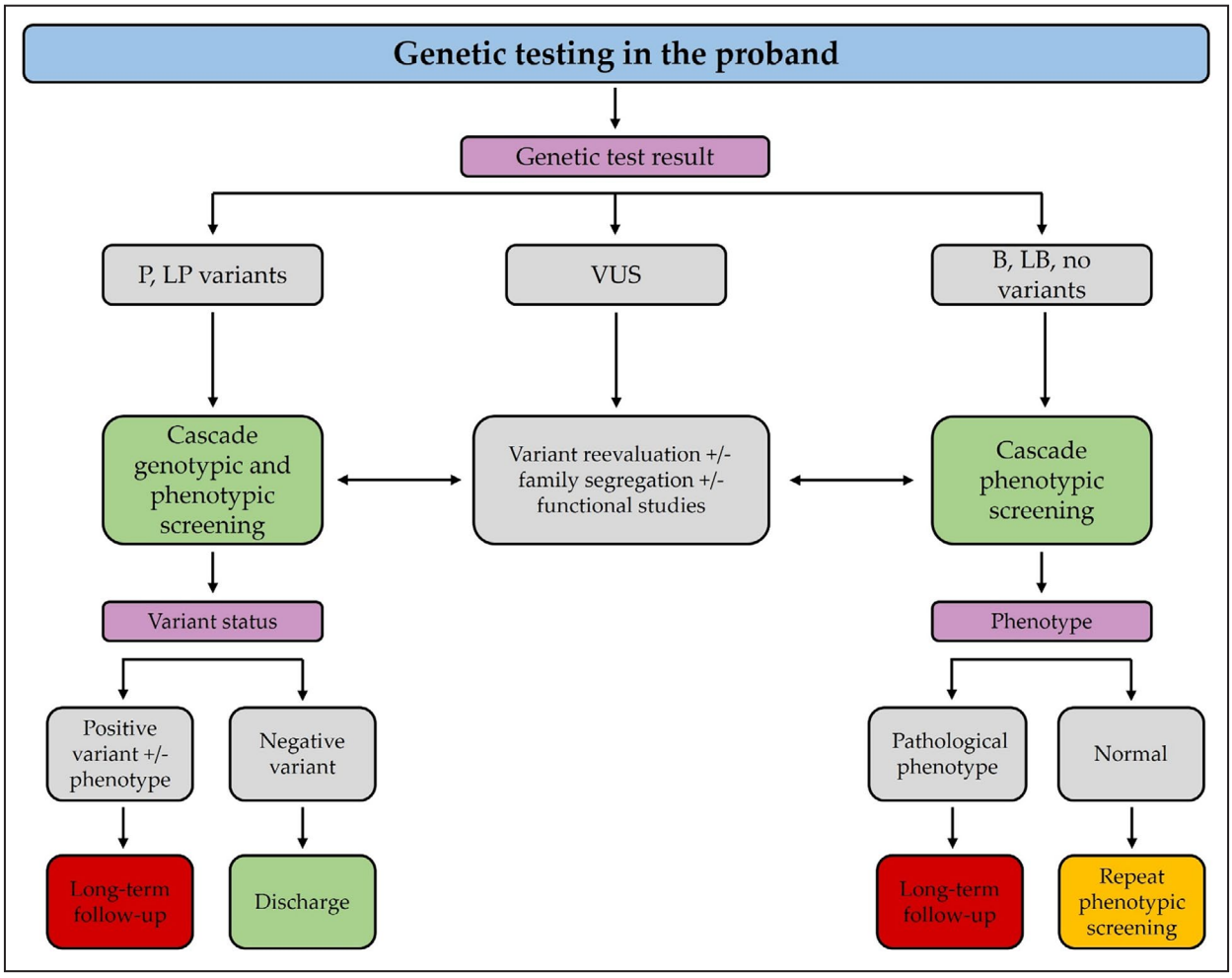

Figure 2. Clinical management strategy based on the results of genetic testing.
B indicates benign variant; LB, likely benign variant; LP, likely pathogenetic variant; P, pathogenetic variant; and VUS, variant of uncertain significance.

a VUS must always consider the gene involved and the family context. For example, a VUS in the *LMNA* gene in a patient with DCM, early conduction disease and family history of SCD may raise stronger suspicion than a similar variant in an unrelated gene.

In some cases, segregation analysis in family members can support or refute pathogenicity, especially if the variant consistently cosegregates with the disease across generations.[96] However, this approach should be guided by genetic specialists, as its value depends on family size, inheritance pattern, and phenotypic clarity.

Functional studies, though not routinely available, can provide decisive evidence in selected cases, such as splicing assays or electrophysiological testing in channelopathies.[97–99] To support interpretation, in silico tools are increasingly used.[100,101] Deep learning models like AlphaMissense[102] or aggregate platforms such as VarChat[103] help predict the pathogenic potential of missense variants using protein structure, conservation, and ensemble scoring systems. These tools offer valuable insight but must be integrated with clinical and genetic data, not used in isolation.

Not only from a clinical standpoint, but also from a research perspective, a VUS may eventually be reclassified as benign, or conversely as pathogenic/likely pathogenic, as additional evidence accumulates over time. This process relies on segregation data from larger pedigrees, functional assays, and aggregation of case reports across centers. Systematic reporting of VUS in research databases is therefore crucial to accelerate recognition and reclassification at a broader level.

WHAT ARE THE LIMITATIONS OF GENETIC TESTING IN TERMS OF PERFORMANCE?

Genetic testing is a powerful tool in cardiology, but it is not infallible (Table S2). One key limitation lies in its technical sensitivity. Even with high-throughput next-generation sequencing, certain potentially actionable variants can be missed.[84] This may happen because of incomplete coverage in difficult genomic regions, limitations in detecting copy number variation, structural or deep intronic variants, or due to mosaicism not captured in peripheral blood.[104] Moreover, not all disease-causing genes are currently known or included in current panels. For these reasons, a negative result does not definitively exclude a genetic cause, especially in patients with a strong phenotype or suggestive family history.

HOW SHOULD I MANAGE PATIENTS WITH A STRONG SUSPICION OF INHERITED DISEASE AND A NEGATIVE GENETIC TEST?

A negative genetic test result does not exclude the possibility of an inherited cardiovascular disease. The genetic architecture of many inherited conditions may be oligogenic, polygenic, or influenced by epigenetic or environmental modifiers, all of which may escape standard testing. When clinical suspicion remains high, due to phenotype, family history, or early-onset presentation, the patient should continue to be managed as "presumed" genetic.[105] This includes:

1. Ongoing structured cardiological follow-up appropriate to the phenotype;
2. Deep family screening based on clinical findings.
3. Clear documentation of the negative result as "inconclusive" rather than "reassuring."
4. Retesting over time may be appropriate, especially as new genes are discovered or as reanalysis tools improve.

In these cases, deep phenotyping is crucial: Advanced imaging, ECG analysis, biomarker profiling, and careful review of extracardiac signs may help refine the diagnosis or identify syndromic forms. For patients with a well-characterized but unexplained phenotype, whole exome sequencing, whole genome sequencing, or participation in selected research registries should be considered.[106]

IS MEDICAL GENETICIST CONSULTATION ALWAYS REQUIRED BEFORE OR AFTER GENETIC TESTING?

While the involvement of a medical geneticist is always valuable, especially in complex or uncertain cases, unfortunately, it is not always feasible for every patient undergoing genetic testing in cardiology.[74] Ideally, universal genetic referral would be optimal; however, given the growing volume of referrals and the limited number of trained specialists, such a model would place an unsustainable burden on genetic services.[107] In many situations, particularly those with a well-defined phenotype, clear inheritance pattern, or known familial variant, genetic testing can be appropriately initiated and interpreted by a cardiogeneticist, provided they are supported by a structured multidisciplinary team.[5] Conversely,

referral to a medical geneticist or dedicated genetics service is strongly recommended when the presentation is atypical or syndromic, when test selection is complex (eg, whole exome sequencing, whole genome sequencing), or when results raise interpretive challenges (eg, VUS, incidental findings, multigene overlap). Their expertise is also essential in addressing reproductive counseling, evaluating de novo variants (often associated with more severe and complex phenotypes), or exploring non-Mendelian inheritance.[108] A triage model, where patients are stratified on the basis of clinical complexity and the potential utility of specialist input, allows for more efficient use of genetic resources. Under this approach, only patients requiring high-level evaluation are referred to a geneticist, while others remain under the care of the cardiogenetics team with access to consultation as needed. Nevertheless, whenever supported by adequate human and financial resources, systematic involvement of a medical geneticist remains the gold standard and the most desirable approach.

WHAT SHOULD I DO IF INCIDENTAL FINDINGS ARE DETECTED?

Incidental findings, also called secondary findings, are genetic results unrelated to the initial indication for testing but with potential clinical significance. These are most commonly encountered during whole exome sequencing or whole genome sequencing, but may also arise from large gene panels that include genes with pleiotropic effects or multisystem involvement.[109] Examples include variants associated with hereditary cancer syndromes and metabolic disorders. While these findings may fall outside the cardiologist's domain, they are often medically actionable and raise important questions about disclosure, responsibility, and follow-up. Before testing, patients must be informed, through pretest counseling, that such findings may occur. Current recommendations from the American College of Medical Genetics and Genomics support returning a list of defined actionable genes when consent is given.[74]

If an incidental finding is identified:

1. The result should be communicated clearly to the patient, with support from a medical geneticist, especially when the condition lies totally outside the cardiologist's expertise.
2. The patient should be referred to the appropriate specialty for further evaluation, surveillance, or preventive intervention.
3. If the finding affects reproductive risk or has implications for family members, genetic counseling and cascade testing should be offered accordingly.

Conversely, genetic testing performed for noncardiac indications may occasionally uncover incidental variants in genes linked to inherited cardiovascular conditions. These findings require cautious interpretation, taking into account gene–disease validity, inheritance patterns, and the possibility of reduced penetrance or variable expressivity. Referral to a cardiogenetics team is crucial to determine clinical significance, guide appropriate surveillance, and coordinate cascade testing when indicated.[109]

HOW CAN A POSITIVE GENETIC RESULT INFLUENCE CLINICAL RISK STRATIFICATION AND PROGNOSIS?

An actionable genetic result can play a critical role in refining risk stratification and prognostic assessment, often complementing traditional clinical tools and enhancing personalized care (Table 3).

As already mentioned, in DCM and nondilated left ventricular cardiomyopathy, actionable variants in genes such as *LMNA*, *FLNC*, *DSP*, *RBM20*, *DES*, and *TMEM43* are associated with a significantly higher risk of malignant ventricular arrhythmias, even when left ventricular ejection fraction is preserved or only mildly reduced. These genotypes are now considered when evaluating the need for ICD implantation, beyond standard ejection fraction thresholds.[5,110] Recently developed gene-specific risk calculators (eg, *LMNA*–ventricular tachyarrhythmia risk score,[111] *FLNC*,[112] *DSP*,[113] and *PLN*[114] scores) further enable genotype-tailored risk stratification. In contrast, truncating variants in *TTN*, while common, are generally associated with more favorable trajectories, including better reverse remodeling and a lower incidence of arrhythmias.[115–118]

In ARVC, genetic confirmation plays a key diagnostic role and aids in distinguishing desmosomal from nondesmosomal forms, which may differ in arrhythmic risk and heart failure progression.[119,120] Although some studies suggest an association between genotype and prognosis, particularly in carriers of multiple or truncating variants, the prognostic impact of a positive genetic test remains variable across cohorts and warrants further investigation.[121] Genetic subtype in ARVC may also influence extracardiac manifestations, such as skin or hair involvement.[122]

In HCM, the prognostic role of genotype is more nuanced. Although sarcomeric mutations do not independently drive ICD decisions, several studies suggest that they may be associated with earlier onset, more pronounced hypertrophy, and greater family penetrance.[55,123,124] Some evidence indicates that *MYH7* variants may carry a slightly worse prognosis than *MYBPC3*, particularly in terms of arrhythmia burden and progression to heart failure, though findings remain heterogeneous across cohorts.[125–127]

Table 3. Illustrative Clinical Vignettes

Inherited heart condition	Clinical case and impact of genetic testing
Case 1: LMNA-related DCM	A 44-year-old man presented with exertional dyspnea (NYHA II) and a family history of SCD (father at 52 y). Echocardiography revealed a dilated left ventricle (LVEDVi 85 mL/m^2) with mildly reduced systolic function (ejection fraction 48%). ECG showed first-degree atrioventricular block and frequent isolated PVCs. CMR demonstrated midwall septal LGE. *Genetic testing identified an actionable truncating LMNA variant*. The LMNA–ventricular tachyarrhythmia risk score (https://lmna-risk-vta.fr/) indicated high arrhythmic risk (12.8% at 5 years). Although ejection fraction was >35%, a primary-prevention ICD with an extravascular lead was implanted to ensure also backup pacing capability, given the high anticipated risk of advanced conduction block despite the patient's young age.
Case 2: DSP-related NDLVC	A 29-year-old woman was referred for palpitations during pregnancy. Echocardiography showed preserved left ventricular size and mildly reduced ejection fraction (53%) with inferolateral hypokinesia. CMR demonstrated extensive mid–basal ring-like late gadolinium enhancement. Holter ECG monitoring revealed NSVT. During pregnancy, she was protected with a wearable cardioverter-defibrillator, without appropriate shocks. *Genetic testing revealed an actionable DSP variant*. The DSP-risk score (https://www.dsp-risk.com/) indicated a high arrhythmic risk (5-y risk of sustained ventricular arrhythmia: 19%). After delivery, a primary-prevention ICD was implanted.
Case 3—*MYH7*-related HCM	A 58-year-old woman, affected by systemic sclerosis, underwent routine evaluation for pulmonary hypertension screening. ECG showed LVH with repolarization abnormalities. Echocardiography and CMR demonstrated symmetric hypertrophy, more pronounced in the septum (17 mm, ejection fraction 65%), no obstruction and subtle septal late gadolinium enhancement, initially attributed to myocardial involvement of systemic sclerosis. Genetic testing, however, *revealed an actionable* MYH7 *variant*, allowing the correct differential diagnosis of HCM and subsequent arrhythmic risk stratification (HCM–SCD risk score: 1.9% at 5 y; HCM–atrial fibrillation risk score: 28% at 5 y). Cascade testing of 3 siblings identified: 1 genotype-negative (discharged from follow-up), 1 genotype-positive with early subclinical hypertrophy on CMR, and 1 genotype-positive/phenotype-negative (scheduled for regular follow-up and lifestyle counseling).
Case 4—*KCNQ1*-related long QT syndrome type 1	An 18-year-old girl experienced recurrent palpitations during swimming. ECG showed a prolonged QTc of 490 ms, confirmed on Holter ECG monitoring, without significant ventricular arrhythmias. Family history was unremarkable. *Genetic testing identified an actionable* KCNQ1 *variant, confirming long QT syndrome type 1*. The 1-2-3 Long QT Risk Score (https://1-2-3-lqt.unipv.it/) indicated a low 5-y risk of life-threatening arrhythmic events (1.98%). She was started on nadolol, with avoidance of QT-prolonging drugs and swimming restrictions. Over 2 years of follow-up, she remained asymptomatic. Cascade testing identified 2 genotype-positive siblings, both enrolled in tailored surveillance programs.

To contextualize genetic concepts in real-world cardiology practice, 4 representative cases highlighting the impact of genetic testing on diagnosis, risk stratification, management, and family screening are provided.

CMR indicates cardiac magnetic resonance; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LVEDVi, left ventricular end-diastolic volume index; LVH, left ventricular hypertrophy; NDLVC, nondilated left ventricular cardiomyopathy; NYHA, New York Heart Association; NSVT, nonsustained ventricular tachycardia, PVC, premature ventricular contraction; and SCD, sudden cardiac death.

Additionally, the presence of multiple actionable sarcomeric variants appears to correlate with more severe phenotypes and worse outcomes.[128] For now, genetic status in HCM is best viewed as a risk modifier, not a stand-alone determinant.

In long QT syndrome, genotype has clear prognostic and therapeutic implications.[129] *LQT1* is generally triggered by exercise and responds well to β blockers, while *LQT2* is more sensitive to emotional or auditory stimuli and has a higher risk of events in young women. *LQT3* typically manifests during rest or sleep and may benefit from sodium channel blockers.[130,131] These distinctions directly influence management and ICD thresholds, by using the dedicated 1-2-3 Long QT Syndrome Risk Score.[132,133]

In Brugada syndrome, the presence of an actionable *SCN5A* variant is associated with a more severe arrhythmic phenotype, slower conduction, and possibly increased risk of SCD, although its role in guiding therapy remains debated.[134,135] In CPVT, mutations in *RYR2* or *CASQ2* confirm the diagnosis and are linked to high arrhythmic risk, especially in the absence of appropriate treatment.[136,137]

In summary, genetic findings serve as important risk modifiers, helping to identify subgroups with higher arrhythmic or progressive disease potential, refine surveillance strategies, and personalize preventive interventions.

WHEN IS THE APPROPRIATE TIME TO TEST ASYMPTOMATIC RELATIVES?

The decision of when to test asymptomatic first-degree relatives should be guided by the specific disease phenotype, the age of onset, and whether early identification would offer a clear clinical benefit. Testing should not be performed automatically in all relatives but, rather, timed to coincide with the earliest age at which clinical surveillance or preventive strategies would be relevant.[15,138]

In adult asymptomatic relatives, cascade genetic testing can generally proceed immediately after appropriate counseling. In contrast, cascade testing in minors is a more delicate decision.[139] The prevailing ethical principle is to defer genetic testing in children unless there is a clear and immediate medical benefit, such as conditions where:

1. Early diagnosis allows initiation of therapy or surveillance.
2. There is a known familial variant associated with early-onset malignant arrhythmias (eg, *RYR2* in CPVT, *KCNQ1* in long QT syndrome type 1).[18]
3. The child participates in competitive sports, and genotype may influence eligibility or risk assessment.[140]
4. There is strong family history of early disease onset or SCD.

This cautious approach reflects respect for the child's future autonomy and aims to avoid unnecessary psychological burden when no immediate clinical benefit exists.

In diseases like HCM or ARVC, where penetrance typically begins in adolescence or early adulthood, testing is often offered from age 10 years to 12 years, though timing may be adapted on the basis of family history. For DCM with later onset (eg, *TTN*), testing in childhood is usually not mandatory and can be deferred, unless clinical signs or symptoms emerge. In all minor cases, deep pretest counseling is essential, as it ensures informed decision making, clarifies the meaning of potential outcomes, and respects the minor's future autonomy.[84,141]

Testing older relatives (aged >70 years) who are asymptomatic, phenotypically negative, and without offspring is typically of limited utility, and cascade screening is better directed at younger relatives who may benefit from early intervention or surveillance.[14]

HOW SHOULD GENOTYPE-POSITIVE/PHENOTYPE-NEGATIVE RELATIVES BE MONITORED OVER TIME?

Individuals who carry an actionable variant but do not yet show clinical signs of disease, so-called genotype-positive/phenotype-negative, require structured surveillance, as they remain at risk for developing disease over time.[142] The timing and severity of phenotype expression depend on the specific gene involved, the inheritance pattern, and modulating environmental or polygenic factors.[143]

The objective of follow-up is to detect early or subclinical signs of disease progression, allowing timely implementation of preventive or therapeutic strategies. Clinical surveillance should be tailored to the underlying phenotype and genotype but in general includes periodic reassessment of symptoms, ECG, Holter monitoring, ergometry and cardiac imaging (echocardiography and/or cardiac magnetic resonance [CMR]). In younger individuals or those from high-risk families, follow-up may be annual, while in lower-risk contexts, longer intervals may be appropriate. Table 4 illustrates the recommended screening intervals based on cardiomyopathy phenotypes.[144] The same screening intervals apply to family members when genetic testing has not been performed or is uninformative in the proband.[138]

In cardiomyopathies, advanced imaging techniques can be particularly useful in identifying early myocardial involvement, even in the absence of overt structural changes.[145] Speckle-tracking echocardiography for global longitudinal strain can detect subclinical systolic dysfunction,[146] while CMR with tissue characterization can reveal early fibrosis or inflammatory activity.[147,148] These subclinical markers may anticipate phenotypic conversion and guide the intensity of follow-up.[149]

In channelopathies, regular ECGs, Holter monitoring, and evaluation of symptoms such as syncope, palpitations, or exertional intolerance are recommended, even when resting ECG is normal. In some cases, lifestyle counseling (eg, avoidance of QT-prolonging drugs, Brugada-triggering drugs, exertion in CPVT) is appropriate even before disease expression.[15]

WHAT ARE THE FUTURE DIRECTIONS IN CARDIOGENETICS?

Cardiogenetics is evolving rapidly, with emerging technologies and paradigms that promise to refine diagnosis, improve risk stratification, and personalize therapy.[150] The future of the field is likely to be shaped by several complementary developments.

Integration of Polygenic Risk Score

While current cardiogenetic practice focuses on monogenic variants, most cardiovascular traits have a polygenic component.[151] Polygenic risk scores, which aggregate the effect of hundreds to thousands of common variants, are being studied as tools to complement monogenic findings, especially in borderline or genotype-negative patients.[152] They may also explain variability in penetrance among carriers and help reclassify VUS.[153] In addition, the integration of artificial intelligence approaches holds promise for improving polygenic risk prediction and assisting in the interpretation of genetic variants in the context of clinical care.[154]

Gene Therapy and Genome Editing

Experimental strategies using viral vectors, antisense oligonucleotides, and Clustered Regularly Interspaced

Table 4. Screening Intervals of Genotype-Positive Phenotype-Negative Relatives According to Cardiomyopathy Phenotypes

Cardiomyopathy	0–5 y	6–12 y	13–19 y	20–50 y	>50 y
DCM/NDLVC	Annually	Every 1–2 y	Every 1–3 y	Every 2–3 y	Every 5 y
HCM	Annually	Every 1–2 y	Every 2–3 y	Every 5 y	Every 5 y
ARVC	Consider once	Every 5 y	Every 1–3 y	Every 2–3 y	Every 5 y
RCM	Annually	Every 1–2 y	Every 2–3 y	Every 3 y	Every 5 y

Modifiers factor	Supporting "intensive" follow-up	Supporting "relaxed" follow-up
Genotype	Especially in DCM/NDLVC: *BAG3, LMNA, RBM20, PLN, FLNCtv, DSP, MYH7*	*TTN*, gene-elusive familial disease
Predominant familial presentation	Sudden cardiac death, severe heart failure	Only structural/electrical abnormalities
Age of first presentation in the family	Age <5 y in relation to affected family member	Age >10 y in relation to affected family member
Findings on cardiac screening	Presence of suspicious structural/electrical findings	Unremarkable cardiac screening

ARVC indicates arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; NDLVC, nondilated left ventricular cardiomyopathy; and RCM, restrictive cardiomyopathy.

Short Palindromic Repeats–based editing are being explored for inherited cardiomyopathies and channelopathies.[155,156] Notably, adeno-associated virus 9–mediated gene replacement for *LAMP2B* in Danon disease has shown promising phase 1 results, with sustained reduction in left ventricular mass and improved functional status.[157] Similarly, gene therapy for *PKP2* in ARVC has entered early clinical trials after preclinical success in halting disease progression and restoring protein expression.[158] While these approaches are not yet in routine use, they raise the possibility of potentially curative interventions, particularly for severe or early-onset genotypes.

Multiomics and Deep Phenotyping

Integration of transcriptomics, proteomics, metabolomics, and epigenetics with genomic data may uncover novel disease mechanisms, clarify genotype–phenotype correlations, identify new therapeutic targets and improve risk prediction or disease monitoring.[159–161] In particular, RNA sequencing may help interpret splicing variants or reclassify VUS.[162]

Expanding Accessibility and Population Screening

As sequencing becomes faster and cheaper, population-scale initiatives may allow presymptomatic detection of at-risk individuals, shifting cardiogenetics from reactive to preventive care.[163] However, this raises challenges in variant interpretation, equity of access, informed consent, and integration into general cardiology practice.[164,165]

CONCLUSIONS

By addressing 20 practical questions, this review aims to equip clinical cardiologists with essential principles of cardiogenetics that are increasingly relevant to daily practice. Recognizing red flags, understanding when and how to initiate genetic testing, and interpreting results within the appropriate clinical context allow noncardiogeneticists to meaningfully contribute to the care of inherited cardiovascular conditions (Table 5). Clinicians are encouraged to develop a practical understanding that supports timely referrals and fosters multidisciplinary collaboration. Empowering the cardiology community with these tools is key to bridging the gap between cardiogenetics and everyday clinical care.

Table 5. Ten Practical Recommendations for Clinical Cardiologists Approaching Genetic Testing in Inherited Cardiovascular Diseases

Do	Don't
Consider genetic testing when the phenotype suggests a heritable disease, especially in younger patients and/or those with family history	Order broad or unselected genetic panels without a defined clinical question or phenotype
Provide pretest counseling, including discussion of possible outcomes (eg, VUS, incidental findings, negative result)	Base clinical decisions on a VUS; these variants are uncertain and not actionable
Refer to a multidisciplinary cardiogenetic team, especially when the phenotype is complex or syndromic or the genetic result is unclear	Assume a negative genetic test rules out an inherited condition, especially with strong phenotype or family history
Offer cascade testing to first-degree relatives only when an actionable variant has been identified	Test asymptomatic minors unless early diagnosis offers clear medical benefit
Integrate genetic findings into long-term management, including arrhythmic risk, reproductive counseling, and tailored follow-up	Manage genotype-positive/phenotype-negative patients as "normal"; they need structured periodic surveillance

VUS indicates variant of uncertain significance.

Key Clinical Take-Home Points

- **When to suspect**: Inherited disease in young patients, those with a family history, clinical/imaging red flags, and/or unexplained cardiomyopathy/arrhythmia.
- **When to refer**: Offer genetic counseling/testing after pretest counseling, particularly in complex or syndromic cases, and only when not clinically futile.
- **How to interpret**: Base management on actionable variants; avoid clinical decisions on VUS; ensure follow-up for genotype-positive/phenotype-negative patients.
- **Multidisciplinary care**: Integrate genetics into long-term management through structured collaboration across specialties.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S2

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