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Role of Genetic Testing in Inherited Cardiovascular Disease
A Review

Allison L. Cirino, MS; Stephanie Harris, MS; Neal K. Lakdawala, MD; Michelle Michels, MD; Iacopo Olivotto, MD; Sharlene M. Day, MD; Dominic J. Abrams, MD; Philippe Charron, MD; Colleen Caleshu, ScM; Christopher Semsarian, MBBS; Jodie Ingles, PhD; Harry Rakowski, MD; Daniel P. Judge, MD; Carolyn Y. Ho, MD

IMPORTANCE Genetic testing is a valuable tool for managing inherited cardiovascular disease in patients and families, including hypertrophic, dilated, and arrhythmogenic cardiomyopathies and inherited arrhythmias. By identifying the molecular etiology of disease, genetic testing can improve diagnostic accuracy and refine family management. However, unique features associated with genetic testing affect the interpretation and application of results and differentiate it from traditional laboratory-based diagnostics. Clinicians and patients must have accurate and realistic expectations about the yield of genetic testing and its role in management. Familiarity with the rationale, implications, benefits, and limitations of genetic testing is essential to achieve the best possible outcomes.

OBSERVATIONS Successfully incorporating genetic testing into clinical practice requires (1) recognizing when inherited cardiovascular disease may be present, (2) identifying appropriate individuals in the family for testing, (3) selecting the appropriate genetic test, (4) understanding the complexities of result interpretation, and (5) effectively communicating the results and implications to the patient and family. Obtaining a detailed family history is critical to identify families who will benefit from genetic testing, determine the best strategy, and interpret results. Instead of focusing on an individual patient, genetic testing requires consideration of the family as a unit. Consolidation of care in centers with a high level of expertise is recommended. Clinicians without expertise in genetic testing will benefit from establishing referral or consultative networks with experienced clinicans in specialized multidisciplinary clinics.

CONCLUSIONS AND RELEVANCE Genetic testing provides a foundation for transitioning to more precise and individualized management. By distinguishing phenotypic subgroups, identifying disease mechanisms, and focusing family care, gene-based diagnosis can improve management. Successful integration of genetic testing into clinical practice requires understanding of the complexities of testing and effective communication of the implications to patients and families.

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Editor's Note
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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Carolyn Y. Ho, MD, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115 (cho@partners.org).

During the past 2 decades, seminal discoveries have identified the genetic basis of important cardiovascular diseases, including hypertrophic and dilated cardiomyopathy (associated with mutations in sarcomere and structural genes),[1] arrhythmogenic cardiomyopathy (associated with mutations in desmosomal genes),[2] inherited arrhythmias (associated with mutations in transmembrane ion channels genes),[3] and Marfan and related syndromes (associated with mutations in genes encoding connective tissue elements).[4] These discoveries have created an important role for genetic testing in the care of families with inherited cardiovascular disease, as reflected in guidelines from numerous professional organizations[5-11] recommending genetic testing to improve the diagnosis and management of patients and at-risk family members. However, many physicians may not believe that they are fully equipped to handle complex genetic results.[12,13] The American Heart Association[14] recently outlined a statement to enhance literacy in cardiovascular genetics for physicians in the genomic era.

This primer provides an overview of the role of genetic testing for inherited cardiovascular disease via the following: highlighting practical considerations to successfully integrate genetic testing into clinical management and focusing on the most common tests for inherited cardiovascular diseases, including multigene panel tests for diagnostic testing and single-variant tests for predictive genetic testing to determine which relatives inherited the family's causal variant. The general principles described apply to most adult-onset mendelian disorders: conditions that typically manifest years to decades after birth and are driven by a single gene defect imparting a large effect.

Table 1. Detection Rates and Clinical Utility of Diagnostic Genetic Testing for Selected Inherited Cardiovascular Diseases

Condition	Major Genes or Gene Families Analyzed[a]	Detection Rate, %[b]	Utility of Genetic Testing		
			Diagnostic Criterion	Effect on Proband Management	Predictive Genetic Testing
Hypertrophic cardiomyopathy	Sarcomere genes	30 to >60	NA	+[c]	Yes
Dilated cardiomyopathy	Sarcomere and cytoskeleton genes (including *TTN*)	30-40	NA	NA	Yes
	LMNA	<5 to 10	Yes	++[d]	Yes
Arrhythmogenic cardiomyopathy	Desmosomal genes	~ 60	Yes	+	Yes
Long QT syndrome	Transmembrane ion channel genes	50-75	Yes	++	Yes
Catecholaminergic polymorphic ventricular tachycardia	*RYR2*, *CASQ2*, *TRDN*, and *CALM1*	50-55	Yes	++	Yes
Brugada syndrome	*SCN5A*	20-25	NA	+	Yes
Marfan syndrome	*FBN1*	>90	Yes	++	Yes
Loeys-Dietz syndrome	*TGFBR1/2*, *SMAD3*, and *TGFB2/3*	70-90	Yes	++	Yes
Familial thoracic aortic aneurysms and dissections	*ACTA2*, *MYH11*, and *MYLK*	20-25	NA	++	Yes
Vascular Ehlers Danlos syndrome	*COL3A1*	~ 95	Yes	++	Yes
Familial hypercholesterolemia	*LDLR*, *APOB*, *PCSK9*, and *LDLRAP1*	60-80	Yes	++	Yes

Abbreviations: NA, not applicable; +may affect management; ++likely affects management.

[a] Represents genes or gene families commonly included on a panel but not a comprehensive list of all genes that could potentially be analyzed.

[b] In general, detection rates are higher if a family history of the condition exists.

[c] Requires differentiating rare phenocopies such as Fabry disease, Pompe disease, or cardiac amyloidosis, with a potential role for risk assessment.

[d] Early indication for an implantable cardioverter defibrillator and/or transplant referral and a high likelihood of conduction disease.

Why Test: Clinical Uses for Genetic Testing

Genetic testing currently is used most frequently in the following situations:

1. Diagnostic testing to identify the underlying genetic etiology in a patient with known or suspected inherited cardiovascular disease.
2. Predictive genetic testing in apparently healthy relatives to determine who has inherited the family's causal variant and is at risk for developing disease.[5-11]

In both situations, genetic testing should begin in well-phenotyped individuals, ideally coupled with comprehensive family evaluation to aid in interpreting and applying results.

Diagnostic Genetic Testing

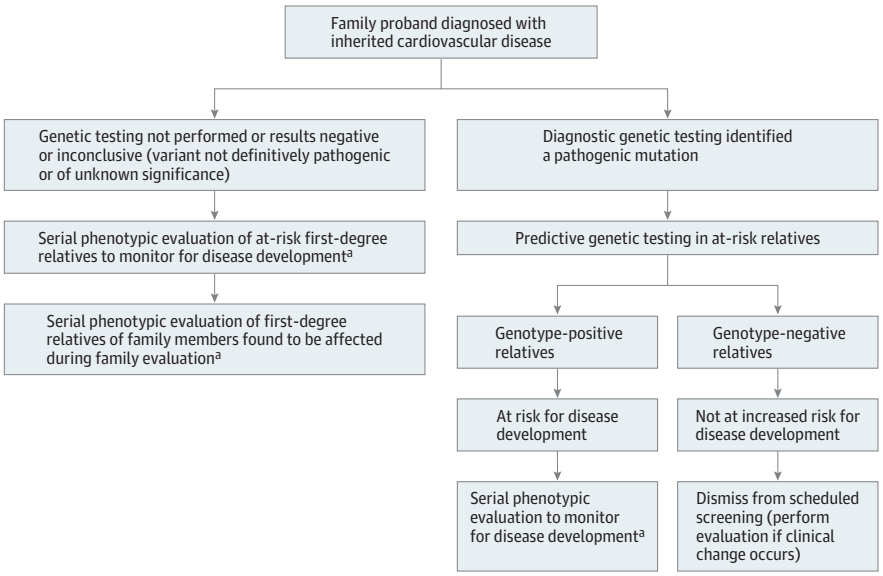
Genetic testing can establish a specific, etiologically based diagnosis. This testing is particularly helpful in situations in which a relatively crude clinical phenotype is shared by multiple conditions (phenocopies), each with a different underlying cause, prognosis, treatment, and implications for family. For example, left ventricular hypertrophy in hypertrophic cardiomyopathy may be difficult to distinguish from athlete's heart, hypertensive heart disease, storage cardiomyopathy (eg, Fabry disease), or infiltrative process (eg, cardiac amyloidosis). Identifying a pathogenic (disease-causing) *GLA* variant in a patient with left ventricular hypertrophy would confirm a diagnosis of Fabry disease and allow for appropriate management, including screening for noncardiac disease manifestations and consideration of enzyme replacement therapy. Likewise, determining the genetic etiology of thoracic aortic aneurysms, which may be a manifestation of syndromic or nonsyndromic conditions, may lead to different thresholds for prophylactic aortic surgery.[9]

Table 1 lists genetic testing available for the most common inherited cardiovascular diseases. In most cases, diagnosis is established phenotypically from clinical cardiovascular testing. However, the presence of a definitively pathogenic variant constitutes a diagnostic criterion for certain conditions, including catecholaminergic polymorphic ventricular tachycardia, Loeys-Dietz syndrome, and Marfan syndrome. Therefore, identification of a pathogenic variant may facilitate a diagnosis in cases in which clinical diagnostic criteria are not completely fulfilled. An important caveat is that genetic testing is probabilistic and may not yield definitively diagnostic results. Results should be correlated with the associated phenotype ideally not just in 1 individual but across the family.

Predictive Genetic Testing and Family Evaluation

For most inherited cardiovascular diseases, the inheritance pattern is autosomal dominant, with a 50% chance of transmission to each offspring regardless of sex. Therefore, evaluation of at-risk healthy family members is recommended. The goals of phenotypic and genotypic family evaluations are to identify individuals with previously unrecognized disease and currently healthy family members who are at risk for future disease development and require longitudinal follow-up.[11] The overall strategy for family screening is summarized in **Figure 1**. Phenotypic evaluation starts with first-degree relatives of affected individuals and is repeated periodically because penetrance (the expression of the clinical phenotype associated with the causal variant) for some conditions may be delayed and diagnostic features may not manifest until adulthood. The frequency and components of longitudinal phenotypic evaluation of at-risk relatives are based on consensus opinion and vary depending on the underlying condition. For inherited cardiomyopathies, longitudinal evaluation of at-risk relatives typically consists of, at a minimum, echocardiography and electrocardiography repeated every 1 to 5 years based on age (most frequently during adolescence and young adulthood). Follow-up should be further tailored on the basis of features relevant to individual relatives or families.

Figure 1. Flowchart of Family Evaluation and Predictive Genetic Testing



The approach to family evaluation after the diagnosis of a genetic cardiovascular disorder is directed by whether a definitively pathogenic variant is found in the family. If so, predictive genetic testing can be performed first to identify relatives who require serial phenotypic evaluation. If not, first-degree relatives are recommended to undergo serial phenotypic evaluation.

[a] Start and frequency are based on age and underlying condition.

If a definitively pathogenic variant in the family has been identified, predictive genetic testing can be pursued to identify efficiently which relatives have inherited that variant and which have not. Relatives confirmed to carry the family's variant are at risk for disease development. They should undergo serial phenotypic evaluation and be informed of the risk for transmission to offspring. Relatives who do not carry the family's variant can be reassured and dismissed from longitudinal phenotypic evaluation but instructed to seek attention promptly if any clinical change occurs.[15,16]

Approaches to predictive genetic testing in children vary in different countries. Concerns center on balancing the potential positive and negative psychological effects on the child of determining genotype when the results of testing may not directly change management.[11,17] Predictive genetic testing can also be used for reproductive planning with prenatal testing during an existing pregnancy to determine whether the fetus inherited the causal variant or through preimplantation genetic diagnosis. Preimplantation genetic diagnosis identifies unaffected embryos, created using in vitro fertilization, for implantation to achieve pregnancy. Predictive testing in the reproductive context is a personal decision that should incorporate consideration of the collective experience of the family as well as the variable penetrance and clinical course associated with most inherited cardiovascular diseases.

In cases in which diagnostic genetic testing is not performed or a causal variant was not identified (results were negative or identified variants that were not definitively pathogenic), predictive genetic testing for healthy relatives is not available. Serial phenotypic evaluation becomes the default strategy, typically starting with first-degree relatives of affected individuals and expanding as new diagnoses are made.

When to Test: Recommendations for Using Genetic Testing

Patients newly diagnosed with an inherited cardiovascular disease should be offered a comprehensive evaluation, including full phenotypic assessment, thorough family history assessment, genetic counseling and testing, and coordinated family evaluation. The **Box** summarizes the process of incorporating genetic testing into clinical care. Not all scenarios have equivalent likelihood of leading to a diagnostic genetic test result. Therefore, identification of situations that are most likely to yield useful results is important.

High Utility

A definitive diagnosis and familial disease increase the pretest probability of positive genetic test results (identification of a disease-causing variant). These results can then have a high utility for family members who can benefit from predictive testing.[18,19]

Intermediate Utility

Absence of a family history does not preclude the use of genetic testing. Genetic forms of cardiovascular disease may be present without affected relatives, owing to recessive inheritance, de novo mutations, or reduced penetrance. Genetic testing should still be considered if results would change the patient's management or when at-risk family members would benefit from testing. In this situation, determining with confidence whether a variant is truly the cause of disease without other affected family members to assess segregation may be difficult (**Figure 2**).

Low Utility

In some scenarios, genetic testing is unlikely to be useful (low likelihood of positive genetic test results and a low predicted clinical effect) and should be deferred. One such example is investigating sudden cardiac death in a family in which no living, affected individuals are available for testing and no DNA is available from affected decedents.[20] Initiation of genetic testing in unaffected relatives is unlikely to yield informative results and may provide false reassurance or lead to incorrect diagnoses.[21] Similarly, in situations in which diagnostic genetic testing has identified an ambiguous result, predictive genetic testing of unaffected relatives is not recommended because the variant may not be a reliable marker for disease risk.

Box. Steps and Considerations for Incorporating Genetic Testing Into Clinical Practice

1. Generate a comprehensive, multigenerational (≥3 generations) family history to
   a. Further understand phenotype in family
   b. Identify at-risk healthy relatives needing phenotypic evaluations
   c. Identify affected relatives and severity of their disease
2. Select appropriate patients and families for genetic testing. Consider
   a. Whether family history of the condition exists
   b. Testing the most severely affected relative with youngest onset
   c. At-risk healthy relatives who would benefit from identification of a causal variant
3. Select appropriate genetic test
   a. If diagnosis is established, select test targeted to that condition
   b. Larger panels may be warranted for overlap or ambiguous phenotypes, with recognition that larger panels may lead to identification of more variants of uncertain significance
4. Engage in and document a thorough informed consent and pretest genetic counseling dialogue with patient, including discussion of
   a. Expected yield
   b. Probabilistic nature of genetic testing and possible categories of results
   c. Possible influence on management, if any
   d. Implications for family members (positive or negative; consider age also)
   e. Potential for variant reclassification
5. Review results and determine appropriate interpretation
   a. Read laboratory interpretation and use laboratory support services
   b. Consider looking at the primary data in references, ClinVar, and other resources
   c. Integrate results with knowledge of the patient and family
   d. Collaborate with genetics professionals
6. Disclose results and provide and document posttest genetic counseling
7. Provide written materials (eg, family letter) or other resources in lay terms that patients can share with relatives to facilitate family communication about test results and recommendations
8. Address management of at-risk relatives
   a. Consider predictive genetic testing in at-risk relatives if genetic testing in the family identified a pathogenic or likely pathogenic variant
   b. If genetic testing was not performed or did not identify a pathogenic or likely pathogenic variant, at-risk relatives may benefit from periodic phenotypic evaluation
   c. If a variant of uncertain significance was identified, consider genetic testing for segregation in other affected relatives to further aid in variant interpretation
9. Establish referral network (eg, mental health professionals for psychology support, specialists for cardiac management, high-risk obstetricians, and social workers)

Whom to Test and How: Selecting the Right Person and the Right Genetic Test

Obtaining a systematic family history and constructing a detailed pedigree of at least 3 generations is an important prelude for managing families with genetic disease (Box).[22] This information will allow comprehensive assessment of the family's phenotype and identification of relatives who would benefit from predictive testing. When possible, information included on the pedigree should be confirmed by medical records or, ideally, by prospective phenotypic evaluation of relatives. Because multiple genetic variants may be present and act synergistically or as disease modifiers, resulting in more severe disease, genetic testing should ideally begin with the family member who is most severely affected and has the most definitive diagnosis. This approach may be logistically difficult owing to geography and accessibility of the family but will maximize the likelihood of identifying all variants relevant to the phenotype in the family.

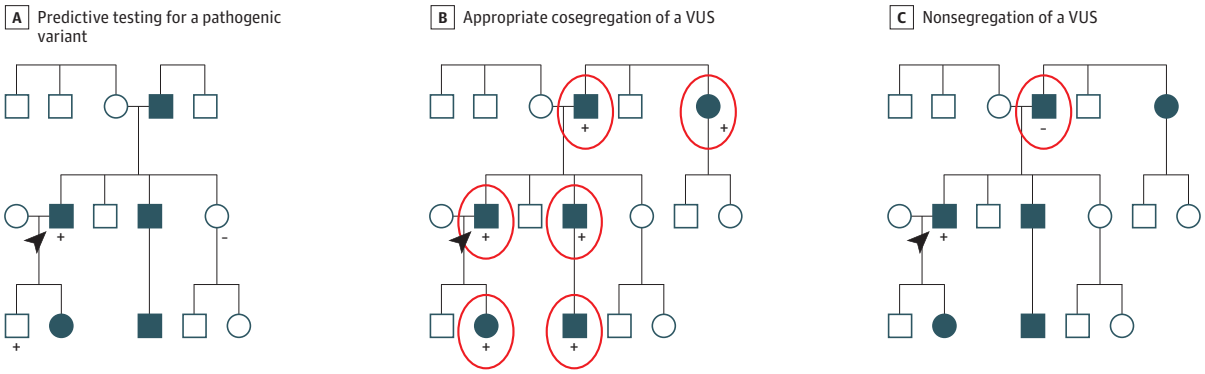
Most inherited cardiovascular diseases exhibit genetic heterogeneity, with mutations in multiple genes causing the same condition. Genetic testing for these conditions is accomplished with multigene panels targeted to a specific phenotype, such as hypertrophic cardiomyopathy, or inclusive of a broader array of genes associated with a number of different conditions that may share overlapping features. For example, current comprehensive panels include more than 90 genes implicated in different types of cardiomyopathy. These broader tests may be more efficient and cost-effective when an equivocal phenotype in the family includes features of more than 1 condition or in families with overlap syndromes, for example, members of a family with coexisting hypertrophic cardiomyopathy, dilated cardiomyopathy, and left ventricular noncompaction. When the phenotype is unequivocal, selection of a panel that is targeted to that particular condition is preferable because broader panels are unlikely to increase clinical yield and may introduce ambiguous results.[23-25]

What the Results Mean: Variant Classification

One of the greatest challenges in multigene panel testing is determining whether an identified sequence variant is the cause of disease. In contrast to traditional laboratory testing, genetic testing is probabilistic in nature[26] and classifies variants along a continuum that reflects the estimated likelihood that a variant causes disease based on the weight of current evidence. Large-scale population-sequencing efforts have highlighted the complexity of the human genome and the remarkable diversity of human genetic variation. Historically, rare sequence variants without other supporting evidence may have been presumed to be pathogenic. However, insights gained from population-sequencing efforts have led to the realization that many benign variants are also rare, prompting a more conservative approach to variant interpretation.[24]

The American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology[27] developed guidelines for variant interpretation that proposed the following 5 tiers of classification: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign. These classifications draw on a variety of evidence types, including population, functional, computational, and segregation data.[27] However, discrepant classifications exist across laboratories for some variants owing to evolving knowledge and practice. New tools have been developed to promote data sharing and improve the interpretation of genetic variants (ClinVar [https://www.ncbi.nlm.nih.gov/clinvar/] and ClinGen [https://www.clinicalgenome.org]). Population-sequencing databases, such as the 1000 Genomes Project,[28] National Heart, Lung, and Blood Institute Exome Sequencing Project Exome Variant Server,[29] Exome Aggregation Consortium,[30] and the Genome Aggregation Database,[30] which include exome- or whole-genome–

Figure 2. Predictive Testing and Segregation Testing in a Family to Assist With Variant Interpretation



Pedigree A shows the use of a pathogenic or likely pathogenic variant identified in an affected relative (arrowhead) for predictive genetic testing in unaffected relatives. The son with the variant (white box with + below) is at risk for disease development, and there is a 50% risk for transmission to each offspring; this individual should undergo longitudinal follow-up to monitor for disease development. The sister without the variant (white circle with − below) is not at risk for disease development, with no risk to offspring and no need for longitudinal follow-up unless clinical change is noted. By contrast, when a variant of uncertain significance (VUS) is identified, segregation testing can be performed to see whether the variant segregates with disease in the family, providing evidence of pathogenicity. Pedigree B illustrates segregation of a VUS with disease in 6 family members, supporting pathogenicity. Pedigree C shows nonsegregation of a VUS in an affected individual, suggesting that the variant is not the cause of disease and should not be used for predictive testing. Square indicates male individual; circle, female individual; filled symbol, clinically affected; +, variant present; and −, variant absent.

Table 2. Variant Classification Categories and Clinical Implications

Implication	Classification				
	Benign or No Variant[a]	Likely Benign[a]	Variant of Uncertain Significance[b]	Likely Pathogenic[c]	Pathogenic[c]
Meaning	No important variants detected; genetic disease cannot be excluded	Variant detected is likely to be harmless; genetic disease cannot be excluded	Ambiguous result; may be reclassified if additional information becomes available	Likely responsible for causing phenotype; family segregation studies may provide additional evidence for causality	Responsible for causing phenotype
Utility for proband	None	None	Unknown	Likely suggests diagnosis; may inform management or lead to additional diagnostic studies	Establishes diagnosis; may inform management
Utility for family	No option for predictive genetic testing; rely on longitudinal phenotypic evaluation	No option for predictive genetic testing; rely on longitudinal phenotypic evaluation	Should not be used for predictive genetic testing; testing affected relatives for segregation may provide evidence of causality	Predictive genetic testing of unaffected relatives should be approached carefully; may be combined with phenotypic evaluation and surveillance	Can be used for predictive genetic testing

[a] Result considered to be negative.
[b] Result considered to be uncertain.
[c] Result considered to be positive.

sequencing data from individuals across diverse ancestries, aid in distinguishing rare, pathogenic variants from benign variants that may be enriched in specific ethnic or racial backgrounds.

Pathogenic and likely pathogenic variants are generally considered to be positive results, meaning that they provide the genetic etiology for disease (**Table 2**). These results may be considered for clinical decision making, including predictive genetic testing. Given the lesser amount of supporting evidence available for likely pathogenic variants, caution is warranted when using these results for predictive genetic testing and the subsequent dismissal of genotype-negative relatives from care. In contrast, likely benign and benign variants are generally considered to be negative results, meaning that they do not provide a genetic etiology for disease.

Variants of uncertain significance are considered to be indeterminate results that should not be used for clinical decision making. A variant of uncertain significance does not provide a definitive genetic etiology of disease and should not be used to determine risk for disease in unaffected relatives. However, testing affected relatives to determine whether the variant segregates with disease in the family can provide valuable evidence to support or dismiss variant pathogenicity (Figure 2). Segregation analysis involves determining whether the genetic variant in question is consistently associated with clinical disease in a family. Because the appearance of appropriate segregation can occur by chance (eg, a child has a 50% likelihood of inheriting any particular allele from their parent), data from a large number of affected relatives or distantly related af-

fected relatives provide stronger evidence that the variant causes disease. On the contrary, observation of a single instance of nonsegregation (a variant of uncertain significance is not present in an affected relative) indicates that the variant is highly unlikely to be the cause of disease, assuming the clinical diagnosis of the relative is not in doubt. Testing affected relatives for segregation aids in the variant interpretation process; however, it may not affect medical management in the family unless the variant is reclassified as having strong evidence for pathogenicity.

Caution should be used when interpreting negative results. Even in cases in which familial disease has been demonstrated, a comprehensive panel may not identify a genetic etiology. Thus, a negative result does not exclude the possibility of genetic disease but indicates that a causative variant could not be identified with the currently available technology and knowledge. Phenotypic evaluation of at-risk healthy relatives is often still advisable. As technology and test offerings advance, additional genetic testing in the proband may be considered at a subsequent stage.

Furthermore, we must recognize that variant interpretation is a dynamic process and that classifications may change over time as additional evidence about the variant becomes available.[24,31] Laboratory practices for reporting updates in variant classification differ and may require the clinician to contact the laboratory and the family again to review the implications of updated information. If a variant has been upgraded to pathogenic or likely pathogenic, predictive genetic testing may be available. If a variant has been downgraded from pathogenic or likely pathogenic to one of uncertain significance, likely benign, or benign, genotype-negative relatives who may have been dismissed from care must be alerted to their potential risk.

To use genetic testing responsibly, clinicians should be aware of the complex, dynamic, and sometimes inconsistent nature of variant interpretation and use the support of genetic testing laboratories and publicly available resources such as ClinVar, ClinGen, and the Exome Aggregation Consortium. Of most importance, genetic data must be integrated with the patient's findings and family history to determine the likelihood that a variant is the cause of disease (Box).

How to Order Genetic Testing and Important Considerations

Pretest and posttest genetic counseling are important steps in the genetic testing process. Such counseling is typically provided by the ordering physician or genetic counselors, specially trained clinicians who facilitate decision making about genetic testing and discuss implications of the results for the patient and family. Pretest counseling provides the information necessary for proper informed consent, including the anticipated yield of testing, the probabilistic nature of genetic testing, how the result will affect the patient's medical management, implications for family members, and the potential for reclassification (Box).[26] Pretest genetic counseling also gives the opportunity to explore potential adverse psychosocial sequela that can result from genetic testing, particularly with predictive genetic testing of children for diseases that typically manifest in adulthood.

Many of the logistical considerations of genetic testing have improved. Turnaround times are decreasing, with results often available in weeks instead of months. Genetic testing laboratories are increasingly accepting different sample types as sources of DNA, including blood, buccal swabs, and saliva. Coverage by third-party payers, including Medicare and Medicaid, varies state by state across the United States. Internationally, national health care systems often provide coverage for genetic testing (eg, Canada, Italy, France, and the Netherlands); however, this is not universally true (eg, Australia). Nonetheless, costs are decreasing, and many laboratories offer financial assistance programs to contain costs to patients.

The concern about the potential for genetic discrimination for those pursuing predictive genetic testing has previously been identified as a disincentive.[32] Now, federal laws in many countries are designed to provide protections against genetic discrimination by health insurance companies and employers, such as the Genetic Information Nondiscrimination Act of 2008 in the United States.[33] Although the same legal protection does not exist for life insurance or long-term care insurance in the United States, protections may exist in other countries. Therefore, individuals should be informed of relevant discrimination risks to evaluate their current insurance coverage before proceeding with testing.

Family Communication

Caring for individuals with inherited disease involves addressing the family as a unit, a particular consideration for genetic testing. For relatives to access genetic testing, a clear and accurate message must be relayed to them. Privacy laws prevent clinicians from directly contacting family members except in cases of imminent danger; therefore, family outreach must be initiated by the patient. When considering the potential for poor psychosocial functioning owing to the challenges of a diagnosis,[34,35] considerable barriers to effective communication of genetic information may exist.[36] Facilitation of this communication is the responsibility of the clinical team ordering genetic testing[37] and may involve the provision of materials written by the clinician that explain the results and recommendations for family members in lay terms (ie, a "family letter"). Development of more innovative solutions to improve family communication may increase the uptake of family screening and genetic testing.

Future Directions: Whole Exome and Genome Sequencing

Broader testing platforms, including whole-exome and whole-genome sequencing, are becoming increasingly available and affordable and may play a larger role in clinical care and biomedical investigation. These tests offer the possibility of discovering new disease genes, thereby providing new insights into disease mechanisms and causal pathways. However, owing to the abundance of genetic variation within an individual genome, the chances for discovery are best when broad genetic testing is coupled with comprehensive phenotypic evaluation of multiple affected relatives or patient-parent trios to aid in distinguishing potential causal variants from background genetic variation that is not clinically significant. The yield of novel gene discovery is unknown; therefore, this opportunity must be balanced against the potential of uncovering genetic information that is unrelated to the indication for testing. The ACMG recommended reporting incidentally identified pathogenic variants in 59 genes considered to be medically actionable.[38,39] Secondary or incidental findings, such as a risk for breast cancer, present challenges to the informed consent process and may lead to additional phenotypic evaluations to understand the implications of the findings.[40] Furthermore, the ACMG list includes genes for inherited cardiac conditions, leading to possible referral of patients to cardiologists for evaluation of these cardiac-related incidental genetic findings. Thus, collaboration with centers with specific expertise in cardiovascular genetics should be strongly considered to help achieve the best outcomes for patients and families.

Conclusions

Genetic testing is a powerful tool in the diagnosis of inherited cardiovascular diseases and identification of at-risk healthy relatives. Owing to constantly increasing availability, cardiologists are now required to be familiar with the myriad of complexities and implications for patients and families. When integrated effectively into clinical practice, genetic testing is an essential step toward individualized medicine and, ultimately, effective prevention of cardiovascular disease.

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Author Affiliations: Cardiovascular Division, Brigham and Women's Hospital, Boston, Massachusetts (Cirino, Harris, Lakdawala, Ho); Department of Cardiology, The Thoraxcenter, Erasmus University Medical Center, Rotterdam, the Netherlands (Michels); Referral Centre for Myocardial Diseases, Careggi University Hospital, Florence, Italy (Olivotto); Cardiovascular Division, Department of Internal Medicine, University of Michigan, Ann Arbor (Day); Inherited Cardiac Arrhythmia Program, Division of Cardiac Electrophysiology, Boston Children's Hospital, Boston, Massachusetts (Abrams); Referral Center for Cardiac Hereditary Diseases, Assistance Publique–Hôpitaux de Paris, Institute of Cardiometabolism and Nutrition, Hôpital de la Pitié-Salpêtrière, Paris, France (Charron); Stanford Center for Inherited Cardiovascular Disease, Stanford, California (Caleshu); Agnes Ginges Centre for Molecular Cardiology, Centenary Institute, University of Sydney, Sydney, Australia (Semsarian, Ingles); Department of Medicine, University of Toronto, Toronto, Ontario, Canada (Rakowski); Division of Cardiology, Johns Hopkins University, Baltimore, Maryland (Judge).

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Study concept and design: Cirino, Harris, Lakdawala, Michels, Olivotto, Day, Abrams, Caleshu, Semsarian, Ingles, Rakowski, Ho.
Acquisition, analysis, or interpretation of data: Lakdawala, Charron, Judge.
Drafting of the manuscript: Cirino, Harris, Charron, Caleshu, Semsarian, Ho.
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