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AHA SCIENTIFIC STATEMENT

Genetic Testing for Inherited Cardiovascular Diseases

A Scientific Statement From the American Heart Association

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ABSTRACT: Advances in human genetics are improving the understanding of a variety of inherited cardiovascular diseases, including cardiomyopathies, arrhythmic disorders, vascular disorders, and lipid disorders such as familial hypercholesterolemia. However, not all cardiovascular practitioners are fully aware of the utility and potential pitfalls of incorporating genetic test results into the care of patients and their families. This statement summarizes current best practices with respect to genetic testing and its implications for the management of inherited cardiovascular diseases.

Key Words: AHA Scientific Statements ■ aneurysm ■ arrhythmia ■ cardiomyopathy ■ cardiovascular diseases ■ channelopathy ■ genetic testing ■ genetics

Genetic testing is informative and useful for the clinical management of various inherited cardiovascular diseases such as cardiomyopathies, arrhythmic disorders, thoracic aortic aneurysms and dissections, and familial hypercholesterolemia (FH). This scientific statement summarizes current best practices for genetic testing in cardiovascular medicine, recognizing that genetic testing methods are evolving and that practices may change. Strategies for genetic testing across these diseases are outlined in Figure 1 (for patients with confirmed or suspected diagnoses of genetic disorders) and Figure 2 (for individuals with secondary or incidental genetic findings). A summary of recommendations for disease-specific genetic testing follows.

SURVEY OF EXISTING LITERATURE

Because there is a dearth of clinical trial evidence for the use of genetic testing in the practice of cardiovascular medicine, this statement draws on the most recent clinical practice guidelines and resources, expert consensus documents, and other scientific statements. These include the American Heart Association statement on enhancing literacy in cardiovascular genetics (2016),[1] the Heart Failure Society of America guideline and American College of Medical Genetics and Genomics (ACMG) resource on genetic evaluation of cardiomyopathy (2018),[2,3] the Heart Rhythm Society/European Heart Rhythm Association statement on genetic testing for channelopathies and cardiomyopathies (2011),[4] a statement on clinical genetic testing for FH (2018),[5] and various publications from the National Institutes of Health–funded Clinical Genome Resource Consortium (ClinGen).[6–10] Of note, various authors of this statement served on and, in some cases, chaired the writing groups for each of these documents.

APPROACH TO THE EVALUATION OF PATIENTS WITH CONFIRMED OR SUSPECTED DIAGNOSES

The Decision to Perform Genetic Testing

All cardiovascular practitioners should be conversant in basic concepts of genetics and have the ability to

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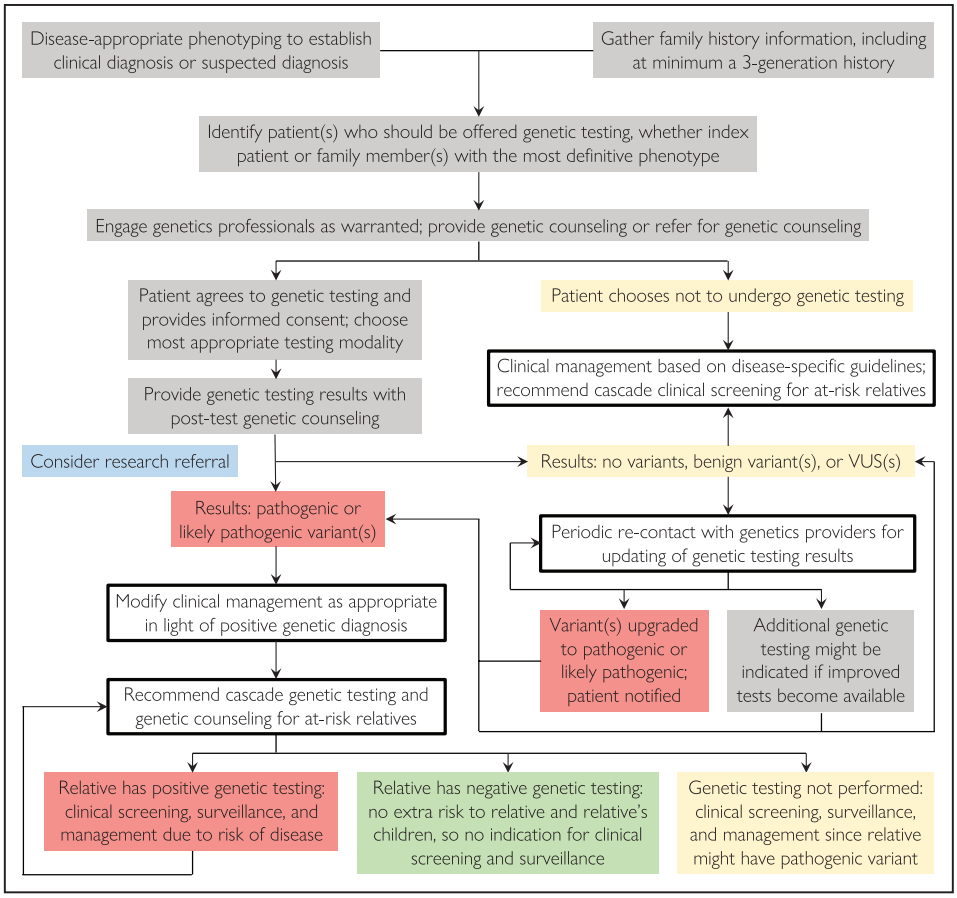

Figure 1. Approach to the evaluation of patients with confirmed or suspected diagnosis of inherited cardiovascular disease.
VUS indicates variant of uncertain significance.

evaluate whether their patients might have genetic cardiovascular conditions. Two recent American Heart Association scientific statements address the core genetics competencies.[1,11] Genetic testing typically should be reserved for patients with a confirmed or suspected diagnosis of an inherited cardiovascular disease or for individuals at high a priori risk resulting from a previously identified pathogenic variant in their family (although similar in meaning, we use the term *variant* in preference to *mutation* in this statement). One crucial element is rigorous, disease-appropriate phenotyping, either by the provider or via referral to a specialist. The second element, which cannot be overemphasized, is a comprehensive family history that spans at least 3 generations. If these 2 elements together establish or strongly suggest an inherited cardiovascular disease, then the next step is to identify the most appropriate person for genetic testing. For reasons of practicality, the provider often will need to test the patient presenting to the clinic first, but in principle, the family member with the most definitive and most severe phenotype should be the one initially tested to increase the chances of identifying pathogenic variant(s) useful for familial testing.

The process of genetic testing differs from traditional laboratory-based testing in that it requires baseline competence in genetic knowledge and practice and typically benefits from interactions between providers and genetics professionals, that is, board-certified geneticists (or cardiovascular specialists with commensurate genetics experience) and genetic counselors.[1] Unless the main provider is sufficiently qualified to choose, order, and interpret the genetic testing and, critically, to counsel the patient appropriately as to the importance and meaning of the genetic test results, referral to a genetics professional is indicated before the test is ordered. After the patient has received pretesting genetic counseling, the patient and the provider can make a shared decision as to whether to undergo testing. As with any medical procedure, the patient should understand the potential benefits, risks, and limitations of genetic testing before consenting to it. In particular, the patient should understand the uncertainties related to the testing, as described in this section and the section "Interpreting and Acting on the Genetic Testing Results," and the implications of the results of genetic testing not just for the patient's own health but also for the health of family members who might share genetic variants predisposing to inherited cardiovascular disease. Providers and patients also should be aware of local laws and regulations—and their limitations—related to genetic testing. For example, in the United States,

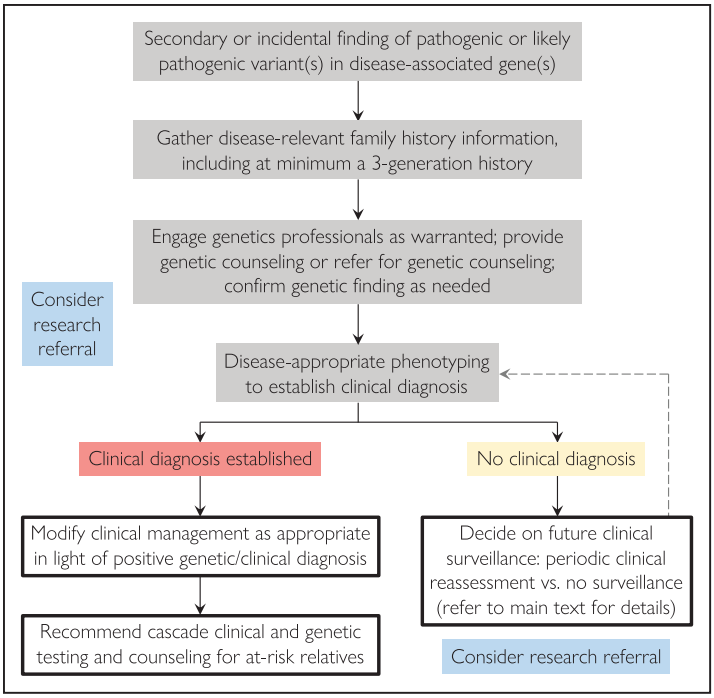

Figure 2. Approach to the evaluation of individuals with secondary or incidental genetic findings.

the Genetic Information Nondiscrimination Act prohibits genetic discrimination (ie, being treated differently because of one's genetic variants) in health insurance and employment, but it does not apply to other types of insurance (eg, life and disability), nor does it apply to companies with <15 employees.

If the decision is made to proceed with genetic testing, the next step is to decide what scope of genetic testing should be performed. Most adult-onset genetic cardiovascular disorders are inherited in an autosomal dominant fashion with variable expressivity and penetrance. The choice of testing ranges from targeted sequencing of a single gene or a few genes most likely to be involved in the disease to large gene panels that include limited-evidence genes to unbiased exome or genome sequencing that queries all genes. The natural temptation might be to test more genes, perhaps all genes, with the thinking that more data are better, especially because next-generation sequencing has made even complete genome sequencing relatively affordable. The additional information might be useful in the research context, that is, improving our knowledge of gene-disease relationships, but panels that include genes with little support for the gene-phenotype association under investigation may not increase the likelihood of clinically actionable results in adult patients.[10,12,13] In addition, expanded test panels may increase the number of variants of uncertain significance (VUSs) identified and, for exome or genome sequencing, may increase the chance of picking up secondary or incidental findings that are not relevant to the disease in question.[14,15] This can lead to confusion and uncertainty. ClinGen is engaged in efforts to develop parsimonious lists of genes with strong evidence linking them to diseases.[8–10,16] Providers should also be aware that genetic testing might not reveal a cause or confirm a diagnosis of the patient's disease because the yield of genetic testing for any inherited cardiovascular disease remains <100%, usually much less than 100%.

If the genetic testing is not performed, the patient should be managed according to the standard of care laid out by contemporary disease-specific clinical guidelines. Because the disease is considered to be genetic in origin but no specific disease-causing variant is known, clinical phenotyping of family members to assess for the disease, that is, cascade clinical screening (in contrast to cascade genetic testing, which is described in the section "Implications of Genetic Testing Beyond the Original Patient"), is typically advisable. Any family members found to have the disease phenotype should be offered genetic testing for themselves.

Interpreting and Acting on the Genetic Testing Results

The return of any genetic testing results to a patient should be accompanied by posttesting genetic counseling, so that the patient has a full understanding of the implications of the results for their health and, potentially, the health of family members. If the testing reveals ≥1 variants in a gene or genes definitively linked to disease, the variants need to be interpreted with respect to their likelihood to cause disease (a process typically performed by genetic testing laboratories, with the interpretations included in the test reports). Given the rapid evolution of the literature and privately held information,

interpretations can vary between genetic testing laboratories and providers and over time.[17] To promote standardization, the ACMG and Association for Molecular Pathology have published a variant interpretation framework that classifies variants into 5 categories: benign, likely benign, uncertain significance, likely pathogenic, and pathogenic.[18]

Recognizing that the ACMG variant interpretation framework is not a one-size-fits-all solution for every gene, ClinGen is engaged in ongoing efforts to modify the framework for specific genes,[7] in part on the basis of data submitted on individual gene variants and their relationships to disease by genetic testing laboratories, clinicians, and researchers to the ClinVar database.[19,20] Each ClinVar submission includes the submitter's interpretation of the variant. Although most variants have concordant interpretations among the various submissions, a significant subset of variants have conflicting interpretations, complicating their use to inform clinical management.

At present, providers are advised to treat variants in a binary fashion. Pathogenic variants and likely pathogenic variants are regarded as positive results; that is, the variants are considered to be causal for disease. Benign variants and likely benign variants are considered to be negative results. Pathogenic and likely pathogenic variants might confirm diagnoses of suspected diseases (ie, serve as major criteria) or warrant changes in clinical management (ie, are actionable) if they occur in certain genes in patients with certain diseases (Table 1).[37] Regardless, the finding of a pathogenic or likely pathogenic variant should prompt an attempt to perform cascade genetic testing of family members (see "Implications of Genetic Testing Beyond the Original Patient").

VUSs are considered neither definitively pathogenic or benign. In some cases, they might indicate a better or worse prognosis but are not considered directly actionable for predictive testing in at-risk family members. For example, in hypertrophic cardiomyopathy, a relatively mature cardiomyopathy phenotype with abundant genetic information available, carriers of a VUS in a sarcomere gene have a prognosis that is intermediate between positive and negative sarcomere gene variant carriers.[38] This observation reflects that the VUS carriers comprise a mix of patients with unrecognized pathogenic variants and patients with unrecognized benign variants. The VUS designation, like any interpretation, is open to reinterpretation at a later date. New information might cause a VUS to be reclassified as a pathogenic or likely pathogenic variant—changing the genetic testing result to a positive one—or to be downgraded to a benign or likely benign variant as variant databases expand.[39,40] Another possibility is that new research might identify novel genes linked to the patient's disease, which might warrant retesting of the patient, especially a genotype-negative patient (ie, a patient without a pathogenic or likely pathogenic variant). Of note, individuals of non-European ancestry are more likely to have VUSs than individuals of European ancestry,[41] a situation that unfortunately is likely to persist until population databases expand further and more accurately reflect patients who undergo genetic testing.

It is the implicit responsibility of patients' providers to ensure that genetic testing is up to date, although formal mechanisms by which providers can ensure that this happens remain to be established. Patients and providers are advised to be cognizant of the need for periodic recontact between them, so that providers are prompted (1) to review genetic testing results (whether by checking with genetics testing laboratories or reviewing the most recent interpretations available in ClinVar, which permits submitters to update their interpretations), (2) to keep patients informed of updates, (3) to recommend additional testing when warranted, and (4) to manage patients appropriately in light of new information.

Implications of Genetic Testing Beyond the Original Patient

Once a patient has tested positive for a pathogenic or likely pathogenic variant in a cardiovascular disease gene, the implications of that variant extend beyond the 1 patient. Providers should always recommend to their patients that they share the genetic risk information with all of their at-risk relatives because any biological relative might share the same variant and either have the disease or be at risk for developing the condition in the future. Privacy concerns (eg, those embodied by the Health Insurance Portability and Accountability Act of 1996 in the United States) restrict the ability of healthcare providers to disseminate information directly to potentially affected relatives without authorization from patients. Providers can make available to patients a summary letter that delineates the genetic finding and is directed toward relatives; these family letters outline accurate information and guide cascade testing. Genetic counselors have expertise in how to provide this information to patients and, ultimately, their family members. Cascade clinical screening and genetic testing for first-degree family members should be offered, along with genetic counseling. For any family member who is found to have the disease or tests positive for the disease-associated variant, first-degree relatives of that individual should in turn be offered testing and counseling. This should continue until all extended family members at risk have been offered clinical screening and genetic testing. Although there might be practical limitations to carrying out full cascade evaluations, especially when relatives have geographic separation or are not in contact, providers should make reasonable efforts to do so.

For at-risk relatives with no current signs of the disease phenotype, periodic clinical surveillance at

Table 1. Genetics-Guided Diagnosis and Management of Cardiovascular Conditions*

Condition	Role in Diagnosis	Role in Management	Source
Vascular disorders			
Familial thoracic aortic aneurysm and dissection	Confirm clinical diagnosis and subtype classification	Causative gene can affect (1) timing of recommended surgical intervention and (2) extent and type of screening for other abnormalities; aids with identification of family members at risk for the condition	Hiratzka et al[21]
Loeys-Dietz syndrome	Major criterion for diagnosis and subtype classification	Confirmed diagnosis can affect (1) timing of recommended surgical intervention and (2) extent and type of screening for other abnormalities; aids with identification of family members at risk for the condition	MacCarrick et al[22]
Marfan syndrome	Major criterion for diagnosis	Confirmed diagnosis can affect timing of recommended surgical intervention	Radke and Baumgartner[23]
Arrhythmic disorders			
Brugada syndrome	Can support clinical diagnosis	Aids with identification of family members at risk for the condition	Ackerman et al,[4] Schwartz et al[24]
Catecholaminergic polymorphic ventricular tachycardia	Major criterion for diagnosis and subtype classification	Aids with identification of family members at risk for the condition	Ackerman et al,[4] Schwartz et al[24]
Long-QT syndrome	Confirm clinical diagnosis and subtype classification	Causative gene may affect recommended treatment/therapeutic decisions and risk assessment; aids with identification of family members at risk for the condition	Ackerman et al,[4] Schwartz et al,[24] Schwartz and Ackerman,[25] Guidicessi and Ackerman,[26] Barsheshet et al[27]
Cardiomyopathies			
ARVC	Major criterion for diagnosis and subtype classification	Aids with identification of family members at risk for the condition	Pinamonti et al,[28] Marcus et al[29]
HCM/DCM	Can support clinical diagnosis and subtype classification	Certain types of variants can be specifically targeted with experimental treatments; aids with identification of family members at risk for the condition	Hershberger et al,[2] Ho et al[30]
Restrictive cardiomyopathy	Confirm clinical diagnosis	Causative gene can guide choice of therapy (eg, transthyretin amyloidosis); aids with identification of family members at risk for the condition	Hershberger et al,[2] Hershberger et al[3]
RASopathy syndromes	Confirm clinical diagnosis and subtype classification	Causative gene can affect extent and type of screening for other abnormalities; aids with identification of family members at risk for the condition	Rauen[31]
Duchenne/Becker muscular dystrophy	Major criterion for diagnosis	Certain types of variants can be specifically targeted with experimental treatments; aids with identification of family members at risk for the condition	Touznik et al[32]
Congenital muscular dystrophy; limb girdle muscular dystrophy; myotonic dystrophy	Confirm clinical diagnosis	Causative gene can affect occurrence, severity, and type of cardiac manifestations (ie, arrhythmias, conduction block, cardiomyopathy); aids with identification of family members at risk for the condition	Beynon and Ray,[33] Wang et al[34]
Emery-Dreifuss muscular dystrophy	Major criterion for diagnosis and subtype classification	Type of variant (missense vs truncating) is important for determining risk of sudden death and need for ICD placement for primary prevention; aids with identification of family members at risk for the condition	van Rijsingen et al[35]
Friedreich ataxia	Confirm clinical diagnosis	Aids with identification of family members at risk for the condition	Corben et al[36]
Lipid disorders			
FH	Can confirm clinical diagnosis	Confirmed diagnosis can affect use and choice of lipid-lowering therapies (eg, improved patient adherence to therapy, earlier initiation of therapy, more aggressive therapy or lower LDL-C targets); aids with identification of family members at risk for the condition	Sturm et al[5]

ARVC indicates arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; FH, familial hypercholesterolemia; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; and LDL-C, low-density lipoprotein cholesterol.

*This is not intended to be a definitive list.

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appropriate intervals, based on the natural history of the disease in question, should be recommended. Relatives who test negative for the variant are typically exonerated from further evaluation or surveillance; their level of risk should be no different from that of the general population. An exception might be if there is concern that the patient is still at increased risk for disease even if the patient is negative for the familial variant; for example, if it

is not certain that the variant is the cause of the disease despite being classified as pathogenic or likely pathogenic, if the clinical phenotype is atypical for the gene variant identified in the family, or if it is possible that an unrecognized variant in another gene might be contributing to disease in the patient. In this scenario, clinical phenotyping and surveillance (typically at a less frequent interval) might be considered.

If a family member chooses not to undergo genetic testing, the uncertain genetic status leaves the disease risk in question. Clinical phenotyping and surveillance are still recommended at intervals similar to those for individuals known to be genotype positive.

Finally, a positive genetic result might be used by a prospective parent for prenatal genetic testing and in the process of preimplantation genetic diagnosis, whereby early-stage embryos are tested for the genetic variant and only those without the variant are implanted by in vitro fertilization, ensuring that the newborn child will not carry the disease-causing variant.

APPROACH TO THE EVALUATION OF INDIVIDUALS WITH SECONDARY OR INCIDENTAL GENETIC FINDINGS

Secondary, or incidental, findings are genetic testing results of relevance for phenotypes or diseases beyond that which triggered the genetic test. (This contrasts with a primary genetic finding that explains disease in a patient tested after already being confirmed or suspected to have disease.) In most situations, the individual, when clinically evaluated, will have no evidence of the expected cardiovascular phenotype implicated by the variant identified by the specific genetic test. This has brought about a new dimension in clinical cardiovascular genetics: what to do with an individual identified with a putatively relevant (and usually disease-causing) variant with no phenotype.

Secondary/incidental findings are becoming particularly relevant because patients are increasingly undergoing genetic testing with exome or genome sequencing in order to maximize the chance of identifying causal pathogenic variants and because costs between gene panels and exomes/genomes are narrowing. Unless analysis of the genetic testing data is deliberately restricted to only genes known to be associated with the disease of interest, pathogenic or likely pathogenic variants in genes unrelated to the disease, for example, a cardiomyopathy gene variant in a patient with cancer being tested for heritable malignancy, might be discovered when that patient does not have and was not undergoing genetic testing for cardiomyopathy. Raising similar issues, healthy people are taking advantage of direct-to-consumer genetic testing services that offer exome or genome sequencing or direct sequencing of the medically actionable genes (see "Implications of Genetic Testing Beyond the Original Patient"). In the absence of disease, the presumed intent is to identify variants that indicate increased risk of future disease.

Table 2. ACMG List of Genes Associated With Cardiovascular Disorders in Which Secondary/ Incidental Findings Are Reportable

Condition	Gene
Ehlers-Danlos syndrome, vascular type	*COL3A1*
Marfan syndrome, Loeys-Dietz syndromes, and familial thoracic aortic aneurysms and dissections	*FBN1*, *TGFBR1*, *TGFBR2*, *SMAD3*, *ACTA2*, *MYH11*
HCM, DCM	*MYBPC3*, *MYH7*, *TNNT2*, *TNNI3*, *TPM1*, *MYL3*, *ACTC1*, *PRKAG2*, *GLA*, *MYL2*, *LMNA*
Catecholaminergic polymorphic ventricular tachycardia	*RYR2*
ARVC	*PKP2*, *DSP*, *DSC2*, *TMEM43*, *DSG2*
Romano-Ward long-QT syndrome types 1, 2, and 3, Brugada syndrome	*KCNQ1*, *KCNH2*, *SCN5A*
FH	*LDLR*, *APOB*, *PCSK9*

ACMG indicates American College of Medical Genetics and Genomics; ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; FH, familial hypercholesterolemia, and HCM, hypertrophic cardiomyopathy.

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The ACMG has published a list of 59 medically actionable genes (known as the ACMG 59) recommended for return in clinical genetic testing that involves exome or genome sequencing.[42] Specifically, the recommendation is that patients should be notified of pathogenic or likely pathogenic variants in any of these genes if they have not opted out of receiving these results. As of this writing, VUSs are not typically returned when discovered as incidental findings. Notably, 30 of the ACMG 59 genes are related to cardiovascular diseases (Table 2).

The recent Heart Failure Society of America/ACMG guidelines have opined on an approach to such individuals who have had secondary findings in cardiomyopathy genes. Identification and notification of a patient of a secondary/incidental finding should prompt a careful assessment for a relevant family history of the disease in question, at minimum a 3-generation history. If the family history is positive, it should immediately elevate the finding to greater concern. Genetics professionals should be engaged if the provider is not sufficiently experienced in genetics. Depending on the provenance of the finding—clinical genetic sequencing versus nonclinical research sequencing—the finding from research sequencing should first be verified by clinical genetic sequencing (eg, a Clinical Laboratory Improvement Amendments–certified test in the United States). Some research laboratories are Clinical Laboratory Improvement Amendments certified and can return medically useful results that do not require clinical confirmation.

On confirmation of the secondary/incidental finding, the patient should undergo a comprehensive assessment

of family history and rigorous, disease-appropriate phenotyping, either by the provider or via referral to a specialist, to ascertain whether the patient has signs of the disease(s) implicated by the finding. If the clinical evaluation establishes a clinical diagnosis, then the patient should be treated similarly to a phenotype-positive, genotype-positive patient with a primary genetic finding (Table 1), and cascade genetic testing with genetic counseling should be recommended for family members. An important distinction between individuals with primary and those with secondary/incidental findings is that in the latter case the individual might be symptom free and have only early signs of the disease. In this case, management should be directed at preventing or halting the progression of disease if the means are available.

In many cases, however, the individual with a secondary/incidental finding has no family history and no signs of the disease in question. In that case, it is incumbent on the provider to assess whether the patient is at risk of developing disease in the future, which can be particularly challenging in children who have a lifetime to manifest disease. Unfortunately, the field has little insight and no published literature to inform this question. In some cases, the likelihood might be very small. For example, the patient might be older than the typical age at onset observed for that particular disease. In other cases, periodic surveillance for signs of incipient disease might be warranted, especially for children or young adults for typical adult-onset diseases. Furthermore, no data are available to inform the practitioner as to whether cascade clinical screening and genetic testing of family members are warranted if no evidence of disease is present in the initial individual with the secondary/incidental finding, especially if the predicted age at onset of the phenotype of concern would likely have shown some evidence of disease. At the time of this writing, the field does not encourage pursuing family-based evaluations when there is no suggestion of disease in the pedigree and the individual with the secondary finding has no evidence of disease. Nevertheless, it should be acknowledged that there is limited experience with this setting, and more will be learned in the coming years. Because more complex situations are possible, tailoring of the approach might be indicated in special circumstances.[3] These complexities highlight the need for pretest genetic counseling to educate individuals about the ramifications of the various outcomes of genetic testing before it is performed.

GUIDANCE FOR DISEASE-SPECIFIC GENETIC TESTING

Genetic Testing for Cardiomyopathies

The 2018 Heart Failure Society of America guideline on cardiomyopathies,[2] a conjoint publication sharing the same writing group as the 2018 ACMG clinical practice resource,[3] offered several recommendations. A family history of at least 3 generations should be obtained for all patients with a primary cardiomyopathy. Second, clinical screening for cardiomyopathy is recommended for at-risk first-degree relatives. Third, patients with genetic, familial, or other unexplained forms of cardiomyopathy should be referred to expert centers. Genetic counseling is recommended for all patients with cardiomyopathy and their family members.

The authors also recommended that genetic testing be offered to all patients diagnosed with all recognized forms of cardiomyopathy (Table 3 lists selected genes associated with cardiomyopathies). In a family, testing should be directed to the most clearly affected family member. If that individual is found to have a gene variant that is judged to be pathogenic or likely pathogenic, then cascade genetic testing for that variant should be offered to at-risk family members. For infants with cardiomyopathy, in addition to any routine newborn screening tests that might have been performed, the specialized evaluation is likely to include genetic testing and should also include an evaluation for syndromic or metabolic conditions for which a specific intervention or therapy might be warranted.

Another recommendation addressed secondary findings: Focused cardiovascular phenotyping should be performed when pathogenic or likely pathogenic variants in ACMG-designated cardiomyopathy genes (Table 2) are identified in an individual. In those individuals, focused cardiovascular phenotyping should be undertaken. If a concordant cardiovascular phenotype is identified, then cascade genetic testing of family members is recommended. If no phenotype is identified, then surveillance screening for the individual should be considered. Even if no phenotype is identified, cascade phenotypic testing of at-risk family members may be considered, depending on the gene in question, the type of variant identified, and its likelihood to be relevant for disease. If family members are found to have evidence of cardiomyopathy phenotypes, genetic testing for the variant may help to establish evidence for disease causality of the variant (ie, segregation).

With respect to specific genes that should be tested in patients with cardiomyopathy, the 2019 gene curation report from ClinGen on hypertrophic cardiomyopathy[10] evaluated 57 candidate genes and judged 8 genes to have definitive evidence and an additional 3 genes as having moderate evidence (Table 3). An additional 12 syndromic genes were judged to be definitively associated with isolated left ventricular hypertrophy (Table 3). Accordingly, clinical genetic testing for patients with hypertrophic cardiomyopathy should include these genes. To date, ClinGen has published a gene-specific variant interpretation framework for just 1 of these genes, *MYH7*.[7] For the other hypertrophic cardiomyopathy genes, the ACMG

Table 3. Lists of Genes to Be Considered for Testing From Guidelines and Statements*

Condition	Genes	Source
HCM, definitive evidence	*MYBPC3*, *MYH7*, *TNNT2*, *TNNI3*, *TPM1*, *ACTC1*, *MYL2*, *MYL3*	Ingles et al[10]
HCM, moderate evidence	*CSRP3*, *TNNC1*, *JPH2*	Ingles et al[10]
HCM, definitive syndromic genes for which isolated left ventricular hypertrophy can be seen	*PLN*, *CACNA1C*, *DES*, *FHL1*, *FLNC*, *GLA*, *LAMP2*, *PRKAG2*, *PTPN11*, *RAF1*, *RIT1*, *TTR*	Ingles et al[10]
DCM	*TTN*, *LMNA*, *MYH7*, *TNNT2*, *BAG3*, *RBM20*, *TNNC1*, *TNNI3*, *TPM1*, *SCN5A*, *PLN*; for testing, all HCM and ARVC genes are recommended to be included	Hershberger et al,[2] Hershberger et al[3]
ARVC	*DES*, *DSC2*, *DSG2*, *DSP*, *JUP*, *LMNA*, *PKP2*, *PLN*, *RYR2*, *SCN5A*, *TMEM43*, *TTN*; consider full DCM panel	Hershberger et al,[2] Hershberger et al[3]
Restrictive cardiomyopathy	*TTR*; consider HCM or DCM panel	Hershberger et al,[2] Hershberger et al[3]
LVNC	Use the gene panel for the cardiomyopathy identified in association with the LVNC phenotype	Hershberger et al,[2] Hershberger et al[3]
Long-QT syndrome	*KCNQ1*, *KCNH2*, *SCN5A*	Ackerman et al[4]
Short-QT syndrome	*KCNH2*, *KCNQ1*, *KCNJ2*	Ackerman et al[4]
Brugada syndrome	*SCN5A*	Hosseini et al[8]
Catecholaminergic polymorphic ventricular tachycardia	*RYR2*, *CASQ2*	Ackerman et al[4]
HTAD, definitive or strong evidence	*ACTA2*, *COL3A1*, *FBN1*, *MYH11*, *SMAD3*, *TGFB2*, *TGFBR1*, *TGFBR2*, *MYLK*, *LOX*, *PRKG1*	Renard et al[9]
HTAD, potentially diagnostic	*EFEMP2*, *ELN*, *FBN2*, *FLNA*, *NOTCH1*, *SLC2A10*, *SMAD4*, *SKI*	Renard et al[9]
FH	*LDLR*, *APOB*, *PCSK9*	Sturm et al[5]
Phenotypic overlap with FH	*LDLRAP1*, *LIPA*, *ABCG5*, *ABCG8*, *APOE*	Sturm et al[5]

ARVC indicates arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; FH, familial hypercholesterolemia; HCM, hypertrophic cardiomyopathy; HTAD, heritable thoracic aortic aneurysm or dissection; and LVNC, left ventricular noncompaction.

*These lists are intended to be illustrative rather than definitive.

criteria for variant interpretation remain the standard,[18] with additional general recommendations provided by ClinGen.[43] ClinGen has not yet published similar curation reports or variant interpretation frameworks relevant to other cardiomyopathies such as dilated cardiomyopathy and arrhythmogenic cardiomyopathy.

The 2018 Heart Failure Society of America and ACMG documents highlighted the need to perform testing of *TTR* in patients with restrictive cardiomyopathy to diagnose transthyretin amyloidosis, given the prevalence of *TTR* mutations in elderly patients with severe heart failure, especially black patients (10% with *TTR* p.Val142Ile allele), and the availability of new therapies to treat amyloidosis.[2,3]

Genetic Testing for Arrhythmic Disorders

The 2011 Heart Rhythm Society/European Heart Rhythm Association expert consensus statement[4] provides the most recent systematic assessment of genetic testing in arrhythmic disorders. The statement addresses the following disorders: long-QT syndrome, short-QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, and progressive cardiac conduction disease (gene lists in Table 3). It recommends cascade genetic testing for family members and appropriate relatives of genotype-positive patients with any of these conditions. It also recommends that genetic testing be offered to patients with a strong clinical index of suspicion for long-QT syndrome, idiopathic QT prolongation with no symptoms and with documented electrocardiographic QTc interval >480 milliseconds (prepuberty) or >500 milliseconds (adults), or a clinical index of suspicion for catecholaminergic polymorphic ventricular tachycardia. Otherwise, the statement holds that, in general, genetic testing can be useful or may be considered in patients with a clinical index of suspicion of 1 of the disorders, with the notable exception of patients with isolated type 2 or type 3 Brugada electrocardiographic patterns, which are not diagnostic for Brugada syndrome and for which genetic testing is not indicated.

The Heart Rhythm Society/European Heart Rhythm Association statement also addresses genetic testing in out-of-hospital cardiac arrest survivors and postmortem testing in sudden unexpected death cases. For cardiac arrest survivors, testing should be reserved for patients with a clinical index of suspicion for a specific cardiomyopathy or channelopathy; otherwise, testing is not indicated. For postmortem testing, the collection of tissue samples for possible future testing is recommended, and the selection of specific testing panels should be guided by autopsy findings, when available, and findings from clinical testing of surviving family members. For either group, in cases with identification

of a genetic cause, cascade genetic testing of family members is recommended. Finally, the Heart Rhythm Society/European Heart Rhythm Association statement recommends against any genetic testing for atrial fibrillation, although more recently published evidence might warrant testing in selected patients.

The 2019 gene curation report from ClinGen on Brugada syndrome[8] evaluated 21 genes implicated in the arrhythmia syndrome. Just 1 gene, *SCN5A*, was judged to have definitive evidence supporting a causal role for the disease. Findings with the other genes should not be used to inform clinical management, although testing of the genes might be useful in the research context. Along the same lines, the 2020 gene curation report from ClinGen on inherited long-QT syndrome[13] evaluated 17 genes and judged just 3 genes—*KCNQ1*, *KCNH2*, and *SCN5A*—as having definitive evidence for typical long-QT syndrome and 4 additional genes—*CALM1*, *CALM2*, *CALM3*, and *TRDN*—as having definitive or strong evidence for long-QT syndrome with atypical features.

Genetic Testing for Thoracic Aortic Aneurysms and Dissections

In 2018, a ClinGen working group summarized the cumulative evidence for 11 genes that cause highly penetrant heritable thoracic aortic aneurysms or dissections (HTADs), with or without syndromic features (Table 3).[9] Eight additional genes with significant evidence for risk associated with HTADs are frequently incorporated into commercial aortopathy testing panels (Table 3). Most families with HTADs with systemic features of Marfan syndrome or Loeys-Dietz syndrome have a pathogenic variant in 1 of these genes. Identification of the causal gene can provide clinically actionable information about associated clinical disorders, aortic disease presentation (age, dissection versus aneurysm), risk for dissection with or without aortic dilation, and risk for additional vascular diseases.[44] For example, patients with pathogenic *ACTA2* variants are also at increased risk for early-onset stroke or myocardial infarction related to vascular occlusive lesions and moyamoya disease.[45] The 2010 American Heart Association/American College of Cardiology guideline for the management of HTADs recommended individualized diagnostic workup and prophylactic interventions based on gene-specific risks.[21] Clinical genetic testing is negative for 70% of families with HTADs who do not present with systemic features, indicating that additional genes remain to be discovered. Therefore, families with HTADs who do not test positive with the current clinical panel of known genes should be considered for referral to research studies.

Table 4. Recommendations and Considerations for Genetic Testing for FH

Genetic testing for FH should be offered to individuals of any age in whom a strong clinical index of suspicion for FH exists on the basis of an examination of the patient's clinical and family histories. This index of suspicion includes the following:
Children with persistent* LDL-C levels ≥160 mg/dL or adults with persistent* LDL-C levels ≥190 mg/dL without an apparent secondary cause of hypercholesterolemia† and with at least 1 first-degree relative similarly affected or with premature CAD‡ or when family history is not available (eg, adoption)
Children with persistent* LDL-C levels ≥190 mg/dL or adults with persistent* LDL-C levels ≥250 mg/dL without an apparent secondary cause of hypercholesterolemia,† even in the absence of a positive family history
Genetic testing for FH may be considered in the following clinical scenarios:
Children with persistent* LDL-C levels ≥160 mg/dL (without an apparent secondary cause of hypercholesterolemia†) with an LDL-C level ≥190 mg/dL in at least 1 parent or a family history of hypercholesterolemia and premature CAD‡
Adults with no pretreatment LDL-C levels available but with a personal history of premature CAD‡ and family history of both hypercholesterolemia and premature CAD‡
Adults with persistent* LDL-C levels ≥160 mg/dL (without an apparent secondary cause of hypercholesterolemia†) in the setting of a family history of hypercholesterolemia and either a personal history or a family history of premature CAD‡

If LDL-C values are unavailable, total cholesterol values ≥320, 260, and 230 mg/dL (corresponding to LDL-C levels ≥250, 190, and 160 mg/dL, respectively) could be used. CAD indicates coronary artery disease; FH, familial hypercholesterolemia; and LDL-C, low-density lipoprotein cholesterol.

*Two or more measurements, including assessment after intensive lifestyle modification.

†Hypothyroidism, diabetes mellitus, renal disease, nephrotic syndrome, liver disease, and medications.

‡Premature CAD: male subjects ≤55 years of age and female subjects ≤65 years of age.

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Genetic Testing for FH

An international expert panel convened by the FH Foundation wrote a scientific statement on clinical genetic testing for FH.[5] This statement generally recommends genetic testing of FH genes (*LDLR*, *APOB*, *PCSK9*, and potentially other genes if warranted by the patient phenotype; Table 3) for individuals with hypercholesterolemia for which an inherited variant is a likely cause. The statement highlights individuals with some combination of persistent elevated low-density lipoprotein cholesterol levels, personal history of premature coronary artery disease, family history of hypercholesterolemia, and family history of premature coronary artery disease who should be offered or may be considered for genetic testing (Table 4). In addition, cascade genetic testing should be offered to all at-risk family members of an individual found to have a pathogenic variant in a FH gene. Genetic testing for FH is expected to result in a higher rate of diagnosis among patients with FH, more effective cascade testing, the initiation of therapies at earlier ages, and more accurate risk stratification.[5]

FUTURE OUTLOOK

The field of clinical genetics is in rapid flux. We anticipate that this scientific statement will need to be updated to reflect new advances in the field and new disease-specific guidelines, expert consensus documents, and other statements that are published. Reliable classification of variants identified in genetic testing will remain a preeminent challenge for the practice of clinical genetics. Ongoing efforts by ClinGen to refine gene-specific variant classification criteria will be critical, as will laboratory-based functional platforms to reliably interpret variants in a medium-throughput or high-throughput fashion.[46,47]

This statement is focused entirely on genetic testing for inherited cardiovascular disorders that are deemed to be largely monogenic in nature (although evidence for these diseases being oligogenic and involving variants in more than just 1 primary causal gene, with the additional variants influencing disease severity, is mounting[48,49]). Complex disorders, that is, polygenic disorders, were not included. Recent reports of polygenic risk scores for complex cardiovascular diseases such as coronary artery disease and atrial fibrillation suggest that patients with extreme scores, that is, in the top few percent of the population, have an increased risk of disease several-fold higher than that of the population average that is equivalent to risk conferred by some monogenic disorders.[50,51] Whether such information is actionable and can meaningfully inform patient management remains to be determined, but with genotyping and sequencing technologies that permit the calculation of polygenic risk scores now being inexpensive enough to be incorporated into routine clinical practice, it is clear that this new frontier in genetic testing will be fertile ground for investigation in the coming years.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on April 24, 2020, and the American Heart Association Executive Committee on June 22, 2020. A copy of the document is available at https://professional.heart.org/statements by using either "Search for Guidelines & Statements" or the "Browse by Topic" area. To purchase additional reprints, call 215-356-2721 or email Meredith.Edelman@wolterskluwer.com.

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Disclosures

Writing Group Disclosures

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Siddharth Prakash	University of Texas Health Science Center at Houston	AHA (Innovative Research Grant)*; NIH (R01)* (neither pertains directly to statement)	None	None	None	None	None	None
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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

After the content for the statement was completed, the chair, Dr Kiran Musunuru, took on the role of chief scientific advisor with Verve Therapeutics in May 2019. The final adjudication steps were led by the vice chair, Dr Ray Hershberger. All subsequent steps were conducted by the entire writing group.

*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
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Joshua W. Knowles	Stanford University	None	None	None	None	None	FH Foundation (FH Foundation is a nonprofit 501c3 organization dedicated to improving the care and diagnosis of patients with FH. I volunteer as their chief research advisor [unpaid]. The FH Foundation receives funding from some genetic testing companies and pharmaceutical companies.)*	None
Daniel J. Lenihan	Washington University in St. Louis	None	None	None	None	None	Pfizer*	None
Anjali T. Owens	University of Pennsylvania	Myokardia (site PI for research study)*; NIH (site PI for research study)*; Array Biopharma (site PI for research study)*	None	None	None	None	None	None

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*Modest.

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