AHA Scientific Statement

Enhancing Literacy in Cardiovascular Genetics

A Scientific Statement From the American Heart Association

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Abstract*—**Advances in genomics are enhancing our understanding of the genetic basis of cardiovascular diseases, both congenital and acquired, and stroke. These advances include finding genes that cause or increase the risk for childhood and adult-onset diseases, finding genes that influence how patients respond to medications, and the development of genetics-guided therapies for diseases. However, the ability of cardiovascular and stroke clinicians to fully understand and apply this knowledge to the care of their patients has lagged. This statement addresses what the specialist caring for patients with cardiovascular diseases and stroke should know about genetics; how they can gain this knowledge; how they can keep up-to-date with advances in genetics, genomics, and pharmacogenetics; and how they can apply this knowledge to improve the care of patients and families with cardiovascular diseases and stroke. (Circ Cardiovasc Genet*****. 2016;9:448-467. DOI: 10.1161/HCG.0000000000000031.)**

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Clinical competence refers to the requirement of health professionals to not only have knowledge of their discipline but to know why, when, and how that knowledge should be applied to improve patient health outcomes. The rapid growth in genetics and genomics knowledge in the recent era has left the clinical community unprepared to apply this knowledge to clinical care. It is important that all health professionals possess core competencies in genetics so that they can systematically and effectively integrate genetics into clinical practice. As such, it is imperative that educational tools and resources be made available to enable the clinician to know when to refer a patient for a genetic evaluation and to acquire sufficient knowledge to understand the findings from these evaluations to help their patients.

Core competencies in genetics for health professionals were published in 2007 by the National Coalition for Health Professional Education in Genetics to guide effective integration of genetics and genomics advances into practice and

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education throughout the professions.[1] This represented a set of competencies in genetics that both geneticists and non-geneticist health professionals considered essential. These competencies can be and need to be adapted to the needs of individual specialty disciplines such as cardiology in which genetics plays a significant role. Although it is unclear at this time exactly how genetically based healthcare delivery will evolve, it will likely be delivered by a combination of genetically trained teams that will include geneticists, genetic counselors, genetics-focused disease specialists, primary care physicians, genetically trained nurses, and nurse practitioners. The relative paucity of trained geneticists and genetic counselors in the workforce is increasing the burden on the clinician and specialist, who is often on the front line of the point of care. Regardless of how the ultimate model evolves, health professionals will require additional training to achieve competence in the application of genetics to medicine.

The purpose of this statement is to provide recommendations about requirements for core competencies in genetics that are relevant to cardiovascular and stroke health and to enable cardiovascular and stroke specialists to acquire these core competencies. This statement derives in part from the National Coalition for Health Professional Education in Genetics guidelines and the Secretary's Advisory Committee on Genetics, Health, and Society report to the US Department of Health and Human Services in February 2011 titled "Genetics Education and Training."[2] The latter includes the genetics education and training needs of point-of-care health professionals, the public health workforce, and patients and consumers, and it provides recommendations to address these needs. The present statement is restricted to recommendations for core competencies in specific areas of cardiovascular genetics that are most often encountered by a cardiovascular practitioner. Many of the resources described apply to practitioners based in the United States; however, the general principles should also be applicable to non–US-based practitioners. The statement does not address graduate and postgraduate training or training of healthcare consumers. The areas of special focus include acquisition of genetics and genomics literacy in structural heart disorders (isolated and syndromic), cardiomyopathies, channelopathies/rhythm disorders, adult-onset cardiovascular disorders, pharmacogenetics, and non-medical issues in genetic care delivery.

Knowledge of these areas will enable the practitioner to identify patients with cardiovascular diseases that may have a genetic basis through history, physical findings, dysmorphology assessment, and known genetic associations; determine when, why, and how genetic testing can be requested for those who require genetic testing; understand when, why, and how cascade screening of family members should be conducted; learn when and why a referral to a geneticist/genetic counselor/genetically trained nurse should be made; understand how genetic test results should be interpreted; determine how findings should be returned to the patient (targeted versus incidental findings, findings of unknown significance); and understand how the health and psychosocial implications of a genetic test result should be addressed. Knowledge about what type of protection is available against discrimination in acquiring health or life insurance to someone at risk for a genetic condition is important. The target audiences are pediatric and adult primary care cardiologists and trainees, pediatric and adult cardiology subspecialists including congenital heart disease specialists, heart failure specialists, electrophysiologists, cardiac interventionalists, preventive cardiologists, stroke specialists, cardiac surgeons, cardiovascular nurses and nurse practitioners, and cardiology-oriented geneticists and genetic counselors.

Core Competencies in Cardiovascular Genetics

Several studies have identified barriers to genetic education, including the following: lack of time; lack of genetics educators to provide education, mentoring, and curricular oversight in residency programs; lack of enthusiasm or interest in genetics and genomics among trainees and practitioners; and lack of educational programs, informational resources, and referral guidelines.[3,4] Despite these barriers, there is a strong imperative to identify competencies needed in applying genetics knowledge to cardiovascular practice, as well as to develop ways to gain and maintain these core competencies. A recent article addressed the issues of genetics and genomics literacy and competencies for pediatricians and other primary care providers in the emerging area of genomic medicine.[5] In addition, the National Coalition for Health Professional Education in Genetics developed a list of core competencies in knowledge, skills, and attitude domains in genetics for all healthcare professionals, as recommended in the Secretary's Advisory Committee on Genetics, Health, and Society 2011 report (Table 1). The basic minimum includes the ability of each healthcare professional to examine their competence on a regular basis and identify gaps in knowledge that need to be addressed, to know when and how to make a referral to a genetics specialist, and to understand not only the health but also the social and psychological implications of genetic findings for individuals and families. The skill sets described in Table 1 are considered universally applicable basic skill sets that will empower the cardiovascular healthcare professional to apply genetic knowledge and practice to the care of their patients. Data Supplement, Table 1 lists simple definitions of commonly used terminologies in clinical genetics.

Role of Trained Genetics Professionals

Genetic healthcare delivery requires close interactions between clinicians and genetics professionals. Genetics professionals in this context refers to board-certified geneticists and genetic counselors. A cardiovascular practitioner should have an understanding of the types of evaluations performed by geneticists, genetic counselors, or advanced practice nurses in genetics to refer patients appropriately. This understanding is critical not only to identify patients who would benefit from additional evaluation but also to relay the importance of this evaluation appropriately to the patient. They should also have knowledge of the genetics professionals in their area. The National Society of Genetic Counselors website[6] can be used to identify genetic counseling professionals by region. A clinical geneticist is a physician who has specific subspecialty training in medical genetics. In the United States, clinical geneticists are certified through the American Board of Medical Genetics

Table 1. Core Competencies in Genetics for Healthcare Professionals

In the knowledge domain, all health professionals should understand:
Basic human genetics terminology
Basic patterns of biological inheritance and variation, both within families and within populations
How identification of disease-associated genetic variations facilitates development of prevention, diagnosis, and treatment options
The importance of family history (minimum 3 generations) in assessing predisposition to disease
The interaction of genetic, environmental, and behavioral factors in predisposition to disease, onset of disease, response to treatment, and maintenance of health
The difference between clinical diagnosis of disease and identification of genetic predisposition to disease (genetic variation is not strictly correlated with disease manifestation)
Various factors that influence the client's ability to use genetic information and services, for example, ethnicity, culture, related health beliefs, ability to pay, and health literacy
The potential physical and psychosocial benefits, limitations, and risks of genetic information for individuals, family members, and communities
Resources available to assist clients seeking genetic information or services, including the types of genetics professionals available and their diverse responsibilities
The ethical, legal, and social issues related to genetic testing and recording of genetic information (eg, privacy, the concern for genetic discrimination for insurance, and in some countries, employment)
One's professional role in the referral to or provision of genetics services and in follow-up of those services
In the skills domain, all health professionals should be able to:
Gather genetic family history information, including at minimum a 3-generation history
Identify and refer clients who might benefit from genetic services or from consultation with other professionals for management of issues related to a genetic diagnosis
Explain effectively the reasons for and benefits of genetic services
Use information technology to obtain credible, current information about genetics
Ensure that the informed consent process for genetic testing includes appropriate information about the potential risks, benefits, and limitations of the test in question
In the attitudes domain, all health professionals should:
Appreciate the sensitivity of genetic information and the need for privacy and confidentiality
Seek coordination and collaboration with an interdisciplinary team of health professionals

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and Genomics. Physicians must have a minimum of 2 years of training in an Accreditation Council for Graduate Medical Education–accredited residency program in another specialty and 2 years in an Accreditation Council for Graduate Medical Education–accredited residency in clinical genetics. Training may also be accomplished as a combined 4- to 6-year residency combined with pediatrics, internal medicine, neurology, or obstetrics and gynecology. The American Board of Medical Genetics and Genomics certifies individuals and accredits training programs in various areas of medical genetics, including clinical genetics, clinical biochemical genetics, clinical cytogenetics, and clinical molecular genetics, as well as in 2 subspecialties in medical biochemical genetics and molecular genetics pathology.[7] Geneticists have expertise in the evaluation, diagnosis, management, and genetic counseling of heritable disease, teratogenic and environmental exposures, genetic syndromes, and metabolic conditions. They also facilitate genetic testing, evaluate at-risk family members, discuss recurrence risk, and provide health supervision management. A genetic counselor is a graduate-level trained healthcare professional who receives instruction in both medical genetics and counseling. Genetic counselors are certified and licensed as clinical care providers. The American Board of Genetic Counseling indicates whether individual practitioners have met the standards necessary to provide competent genetic counseling services.[8]

The National Society of Genetic Counselors describes genetic counseling as the process of helping people understand and adapt to medical, psychological, and familial implications of genetic contributions to disease. This process integrates the following: (1) interpretation of family and medical histories to assess the chance of disease occurrence or recurrence; (2) education about inheritance, testing, management, prevention, resources, and research; and (3) counseling to promote informed choices and adaptation to the risk or condition.[9] Referral to a geneticist is appropriate to generate a differential diagnosis and to diagnose, manage, and treat disease. Referral to a geneticist or genetic counselor is appropriate for pedigree evaluation and risk assessment, facilitation of genetic testing, and explanation of genetics principles or the testing process. Table 2 indicates reasons for referral for genetic evaluation.

As genetic applications expand, there is a need for a multidisciplinary team of experts that includes not only board-certified genetic professionals but also clinicians and nurses with disease-specific genetic expertise. The relative paucity of trained genetics professionals spurred the creation of a new international nursing certification in genetics in 2015, the American Nurses Credentialing Center advanced genetics nursing board certification through portfolio assessment. Certification through portfolio is a new assessment methodology to achieve American Nurses Credentialing Center board certification that assesses the skills and knowledge of an advanced practice nurse to practice in genetics and genomics through the review of a collective body of work present in a nurse's portfolio after initial registered nursing licensure and graduate education. A registered nurse or nurse practitioner who completes the eligibility requirements and successfully passes the portfolio review process is awarded the credential Advanced Genetics Nursing-Board Certified (AGN-BC), which is renewable every 5 years. The AGN-BC nurse can perform risk assessment, analyze the genetic contribution to disease, discuss the impact of risk on healthcare management for individuals and families, provide genetics education, and conduct research in genetics as part of a multidisciplinary team.[10] There is a need for similar

Table 2. Characteristics of Patients Who Benefit From Genetics Referral and Evaluation

Indication for Referral	Goals of Referral
Suspicion of an underlying genetic syndrome with multisystem involvement:	Syndrome diagnosis, care coordination, and implementation of health supervision guidelines
Intellectual or learning disability; autism; other cognitive impairment	
Dysmorphic features	
Short stature	
Features of connective tissue disease	
Any congenital anomaly	
Endocrine abnormalities	
Sensory deficits such as hearing loss or visual impairment	
Neurological deficits or psychiatric illness	
Unexplained medical conditions	
Family history of heritable cardiac conditions, including congenital heart disease, cardiomyopathy, aortopathy, heritable arrhythmias, familial hyperlipidemia, and sudden cardiac death	Genetic evaluation, testing, diagnosis, counseling of patient and family
Isolated congenital heart disease highly associated with specific genetic conditions (eg, interrupted aortic arch, truncus arteriosus, supravalvular aortic stenosis)	Genetic evaluation, testing, diagnosis, and counseling of patient and family
Patient or parent interested in discussing recurrence risk for offspring before pursuing pregnancy	Preconception or prenatal genetic counseling regarding recurrence risk, options for preimplantation genetic diagnosis
Facilitation of genetic testing; pretest or posttest genetic counseling	Explanation of possible outcomes of genetic testing
	Discussion of GINA, other insurance issues
	Provision of educational resources and anticipatory guidance after a positive genetic test result

GINA indicates the Genetic Information Nondiscrimination Act.

board-certified programs for physicians to prove expertise in disease-specific genetics, as well as a need for continuing medical education programs to ensure maintenance and enhancement of their skill sets.

The provision of genetic services, access to genetics professionals, and referral patterns can vary by institution, location, available expertise, and disease type. In some countries, standardized referral patterns and infrastructure exist for genetic evaluation for conditions such as heritable cardiomyopathies and channelopathies, but in the United States this has not been uniform, and there is currently no single model for delivery of care.[11,12] The benefits of evaluation by a geneticist and incorporation of genetic counseling have been demonstrated for many cardiovascular genetic conditions.[13–15] The complexity of current cardiovascular genetic evaluation and testing has led to guidelines recommending evaluation in centers with specialized expertise whenever possible to facilitate access to multidisciplinary teams that include cardiovascular clinicians, geneticists, and genetic counselors.[16,17] The expertise in the practice of any medical specialty is acquired not only through certified training but equally importantly through practical experience and patient interactions. This is particularly true of genetic medicine, in which a genetic practitioner is required to keep pace with rapidly emerging technologies and is required to treat not only the individual but the family of the individual. The degree of genetics expertise required can vary considerably depending on the disease and the type of genetic testing. For example, genetic counseling, evaluation, and genetic testing for syndromic and heritable cardiovascular diseases usually require close collaboration with a genetics professional, but pharmacogenetic testing can be employed by care providers who maintain an up-to-date knowledge of the field.

What the Cardiovascular Practitioner Needs to Know

This section details cardiovascular conditions that require genetic evaluation and issues to be considered before and after genetic testing. It includes content-specific knowledge and expertise aimed at a practicing cardiovascular healthcare professional. Focus areas include cardiomyopathy, congenital heart disease, channelopathies/rhythm disorders, valvular and vascular disorders, cardiovascular pharmacogenetics, and emerging genomic technologies and applications.

When Do I Suspect a Genetic Condition?

Almost all cardiovascular diseases have been identified as having genetic contributors, and every cardiovascular clinician should have the basic skill sets to suspect a genetic condition. It is important for practicing cardiovascular clinicians caring for children and adults to recognize when a prompt and accurate genetic diagnosis might influence the medical and surgical care of these patients. This section first discusses important aspects of the clinical evaluation that should be performed to recognize a potential genetic condition and subsequently reviews common cardiovascular conditions that are known to have significant genetic contributors and might warrant further genetic evaluation or testing.

Although all patients receive a complete history and physical examination at the time of the initial evaluation by a cardiovascular practitioner, it is important for the clinician to be aware of several key findings that may be suggestive of a genetic disorder (Table 3). As part of the clinical evaluation, the presence of developmental delays or intellectual disability and associated birth defects and other congenital anomalies suggests a genetic syndrome that requires genetic evaluation.

The importance of a 3-generation family history cannot be overemphasized and should be obtained in all patients regardless of the type of cardiovascular disease, with special emphasis on a history of congenital malformations, including

Table 3. Clinical Findings Suggestive of a Cardiovascular Genetic Disorder

Cardiac disorder with associated developmental delay/intellectual disability
Congenital heart defect with additional birth anomalies
Congenital heart defect with dysmorphic facies
Positive family history of multiple closely related individuals affected with the same condition
Affected offspring of a couple with ≥3 pregnancy losses
Conotruncal heart defects, supravalvular aortic stenosis, bicuspid aortic valve Thoracic aortic aneurysm or dissection
Unexplained cardiomyopathy
Family history of sudden cardiac death in a previously healthy person
Abnormal ECG findings consistent with inherited arrhythmia

ECG indicates electrocardiography.

congenital heart defects (CHDs), spontaneous miscarriages, cardiomyopathy, and sudden cardiac death (SCD). Several resources for pedigree capture exist, and "My Family Health Portrait," developed by the Office of the Surgeon General, is one such tool that can be completed by the patient before the clinic visit to assist in the generation of a family pedigree.[18] A complete family history is often the first clue to the presence of a genetic or inherited disorder.

Congenital Heart Defects

An estimated 25% to 30% of CHDs are considered to be "syndromic" because they occur in well-described genetic syndromes caused by chromosomal aneuploidy, chromosomal microdeletions/microduplications, complex chromosomal rearrangements, or even single-gene mutations.[19] Common genetic syndromes associated with CHDs include trisomy 21 (Down syndrome) and 22q11.2 deletion syndrome (DiGeorge or velocardiofacial syndrome).[20] Advances in genetics have resulted in the identification of the molecular basis of many of these genetic syndromes.[21] Therefore, genetic evaluation is recommended in all patients with CHDs accompanied by extracardiac malformations or neurodevelopmental abnormalities. Data Supplement, Tables 2 and 3 enumerate common syndromes associated with CHDs.

As genetic causes for CHDs are increasingly recognized, the line between syndromic and nonsyndromic disorders is becoming less clear, particularly because some syndromic causes can have very subtle features that are easy to miss. Nonsyndromic CHDs can have a significant genetic component and should be suspected, especially if there are additional affected family members.[22] Numerous genes have been identified that are associated with specific types of nonsyndromic CHDs.[21] For example, whereas supravalvular aortic stenosis is commonly seen in Williams-Beuren syndrome, caused by deletion of the 7q11.23 region that encodes the elastin (*ELN*) gene, nonsyndromic supravalvular aortic stenosis should prompt testing for single-gene mutations in the *ELN* gene. Similarly, because of the significant association of malformations of the cardiac outflow tract (conotruncus) and aortic arch and the significant phenotypic variability in 22q11.2 deletion syndrome, it has been advocated that all infants with interrupted aortic arch type B or truncus arteriosus, as well as a subset of patients with tetralogy of Fallot (with associated absent pulmonary valve syndrome, aortic arch anomalies, pulmonary artery anomalies, and aortopulmonary collaterals), be tested for this deletion independent of the presence of extracardiac features.[20] In clinical practice, infants with these diagnoses are often treated as if they have 22q11.2 deletion syndrome while the results of genetic testing are pending, especially at times of surgical intervention. The 2007 American Heart Association Scientific Statement on the "Genetic Basis for Congenital Heart Defects" provides a comprehensive overview of both syndromic and nonsyndromic conditions associated with CHDs.[20]

Knowledge of heritability is important not only to prompt genetic evaluation of the proband but also to guide screening of first-degree relatives. For example, malformations of the left side of the heart, including bicuspid aortic valve, aortic coarctation, and hypoplastic left heart syndrome, are known to be highly heritable, with a CHD prevalence of ≈20% or higher among affected first-degree relatives.[23,24] Accordingly, echocardiographic screening of first-degree relatives of patients with left-sided defects has been recommended in the 2008 American Heart Association/American College of Cardiology "2008 Guidelines for the Management of Adults With Congenital Heart Disease."[25]

Thoracic Aortic Aneurysms

Thoracic aortic aneurysms often occur in the setting of genetic syndromes such as Marfan, Loeys-Dietz, Ehlers-Danlos, or Turner syndrome, each of which have specific clinical phenotypes and specific genetic origins.[26] Isolated (nonsyndromic) thoracic aortic aneurysms can also have a genetic basis, and accurate genetic diagnosis can have important implications in clinical management, even in the adult[26–28] (Data Supplement, Table 4). These conditions are most frequently inherited in an autosomal dominant fashion, such that a diagnosis has significant implications for first-degree relatives. There are published guidelines that specifically address cardiac screening and genetic testing in first-degree relatives.[26]

Cardiomyopathy

Cardiomyopathies encompass a heterogeneous group of diseases that affect the myocardium and result in mechanical or electrical dysfunction and exhibit inappropriate ventricular hypertrophy, restriction, or dilation.[29] The cardiac practitioner should be aware of the phenotypic types of cardiomyopathies: hypertrophic cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, and left ventricular noncompaction cardiomyopathy.[30,31] Genetic evaluation is recommended both in primary and in secondary cardiomyopathies (syndromic, metabolic or mitochondrial, neuromuscular). The first-line genetic testing in an affected proband with isolated cardiomyopathy is usually a gene panel targeted to the cardiomyopathy subtype. These panels predominantly include sarcomeric genes important in myocyte structure and function. However, given the considerable overlap in genes associated with the various cardiomyopathy phenotypes, expanded gene panels that include all cardiomyopathy-associated genes are being

used increasingly if targeted panels yield negative results or as first-line testing in patients with nonhypertrophic cardiomyopathies. As with thoracic aortic aneurysm, the diagnosis of cardiomyopathy in an individual has significant implications for first-degree relatives. Guidelines for cardiac screening and genetic testing exist for nonsyndromic, nonmetabolic cardiomyopathies.[17]

Channelopathies/Arrhythmias

Over the past several decades, the role of genetic contributors has become increasingly recognized in rhythm disorders. For the general cardiovascular practitioner, it is important to recognize the genetic basis of several inherited arrhythmias, which include long-QT syndrome (LQTS), Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, and short-QT syndrome. In the young, LQTS is an important cause of SCD caused by ventricular arrhythmias, generally attributed to torsade de pointes.[32] It is inherited in an autosomal dominant manner, and numerous genes have been identified. Although LQTS most often occurs in an isolated manner, it can occur in the setting of well-described syndromes including the autosomal recessive Jervell and Lange-Nielsen syndrome (with associated congenital deafness), Andersen-Tawil syndrome (with periodic paralysis, dysmorphic facies, and malformations), and Timothy syndrome (with cardiac and other birth defects and autism). Brugada syndrome is a cause of familial idiopathic polymorphic ventricular tachycardia or fibrillation and SCD for which numerous genes, most leading to reduced cardiac sodium current, have been identified. It is characterized by the electrocardiographic findings of ST-segment elevation in the anterior precordial leads and a structurally normal heart.[33] Another inherited arrhythmia is catecholaminergic polymorphic ventricular tachycardia, which usually presents with syncope, ventricular tachycardia (often of several morphologies), and SCD with exercise or emotional stress.[34] The more common form of catecholaminergic polymorphic ventricular tachycardia occurs in an autosomal dominant manner because of mutations in *RYR2*, and the recessive condition is caused by mutations in *CASQ2*. Short-QT syndrome is a more recently described inherited arrhythmia. It is characterized by a short QT interval on the electrocardiogram and a clinical history significant for atrial fibrillation, ventricular fibrillation, or SCD.[35] Gain-of-function mutations in potassium channel genes previously implicated in LQTS have been associated with short-QT syndrome. Diagnosis of these conditions at any age should prompt a genetic evaluation. Again, the diagnosis has significant implications for first-degree relatives.

When Do I Refer for Genetic Testing?

A key skill set is to know when to refer a patient to a genetic professional and what kind of clinical genetic testing is available. Once the practitioner suspects a genetic condition, the next step is to engage genetics professionals and explore options for genetic testing if available. It is important that the practitioner be aware of the structured, tiered approach to genetic testing. The process of genetic testing involves identifying the most appropriate person in the family to test, selecting the most appropriate genetic test, and discussing testing options and outcomes, including positive, negative, and uncertain results. Before referral, a practitioner should discuss the reason for referral and the goals (eg, diagnosis, management, genetic testing, risk assessment, or prenatal counseling) with the patient.[13,36] Predictive testing, genetic testing in children, and prenatal testing are types of genetic testing that require additional domain-specific knowledge.[37,38]

Who Should Be Tested

Testing should be offered to an affected family member first. In the event of a positive genetic test, cascade screening of the specific mutations can be performed in other family members to identify those at risk. It is important to appreciate that many genetic tests inform likelihood of disease and are not usually the sole determinant of disease status. The care provider needs to be able to accurately assess the results from genetic testing in the context of the patient's clinical phenotype, as well as the patient and family history. In many cases, this is best achieved with the help of a multidisciplinary collaborative team.

Types of Gene Testing

A basic understanding of genetic testing technology and diagnostic yield of these tests is important because this affects both test choice and interpretation (Data Supplement, Table 5). There are many types of genetic tests, and the best option will depend on the specific cardiovascular condition. For patients with multiple congenital anomalies suggestive of a possible chromosomal rearrangement, a chromosomal analysis for trisomies, monosomies, sex chromosome abnormalities, large chromosomal deletions/duplications, and translocations is often first-line testing. Of late, this test has largely been replaced by chromosomal microarray analysis, which is far more sensitive and can detect very small deletions/duplications (which might involve only part of a gene or a small region between genes). Microarray analysis has also been used in place of fluorescence in situ hybridization analysis to diagnose deletion disorders such as the 22q11.2 deletion syndrome and 7q11.23 microdeletion (Williams-Beuren) syndrome. The high sensitivity of the chromosomal microarray approach, however, has led to increased detection of small deletions/duplications with unknown clinical significance.[39]

Gene sequencing is the test of choice to identify genetic variation at the nucleotide level.[37,40–44] For the cardiomyopathies, different gene panels have been designed based on the cardiac phenotype, although with the overlap of phenotypes and the ability of mutations in the same gene to lead to a variety of phenotypes, there is an increased reliance on pan-cardiomyopathy panels that include genes associated with the full spectrum of cardiomyopathies. Recent reports, however, suggest that the diagnostic yield of expanded panels depends on the cardiomyopathy subtype. For example, expanded gene panels might not substantially increase the diagnostic yield in hypertrophic cardiomyopathy patients compared with smaller gene panels,[45] but an expanded gene panel can increase the yield of pathogenic or likely pathogenic variants in adults with dilated cardiomyopathy.[46] Therefore, the optimum approach to cardiomyopathy testing is still evolving. Although there are

several gene panels for cardiomyopathy genes, there are very few CHD genes for which clinical testing is currently offered.

If targeted gene sequencing does not reveal a disease-causing mutation, follow-up testing might include restricted microarray-based testing to identify a deletion or duplication of all or part of a gene or next-generation sequencing that explores the exome (coding regions) or the whole genome (coding and noncoding regions). Dropping costs and turnaround times have resulted in increased adoption of clinical exome or genome sequencing as second-line testing for gene-elusive disorders. Clinical exome or genome sequencing requires robust bioinformatics pipelines to detect a true positive signal from noise. However, the bioinformatics pipeline can differ among laboratories, which results in discordant results for the same patient depending on the laboratory doing the testing. It is important for the person who orders the testing and receives the results to be aware of these limitations. In addition, although a nontargeted approach is more comprehensive and unbiased, it can lead to the identification of variants in genes that are either of uncertain significance or are linked to unrelated medical conditions. The dilemma of how to address such findings of "uncertain significance" and "incidental" findings is addressed in Managing Genetic Test Results. Additionally, the diagnostic yield on these tests is greatly influenced by the extent of coverage of genes of interest and the depth of sequencing (ie, number of times a nucleotide is read during sequencing). The higher the depth and better the coverage of the genomic regions, the more reliable the findings. A recent study reported considerable variability in the coverage of known cardiac genes depending on the types of sequence capture kit and depth of sequencing used.[47] Sequence capture is the process of enrichment of selected genomic regions from whole genomic DNA and is required to capture the coding regions of the genome when exome sequencing is performed.

When referring patients for genetic testing and evaluating the results of a particular genetic test, it is important to understand the strengths and limitations of the testing format. Especially in the case of a "negative" genetic test, it is important to understand what has not been examined and therefore cannot be excluded, as well as the fact that even when the clinical diagnosis is secure, the diagnostic yield for some conditions can be <50%, in part because of genetic heterogeneity (Table 4). Therefore, a negative genetic test in an index case does not exclude a genetic cause, and clinical screening of family members is still required. Most important, given the potential psychosocial implications of genetic testing in asymptomatic and phenotype-negative individuals, genetic testing should only be offered with proper genetic counseling.

Managing Genetic Test Results

When a genetic test result is returned to the ordering practitioner, the genetic testing service will indicate whether a genetic variant has been identified. In addition, the service will assign a level of certainty as to the likelihood that the observed variant is responsible or causal for the suspected condition. To make sure that all genetic testing services use similar practices to assign the level of certainty, the American College of Medical Genetics and Genomics (ACMG) has developed a 5-category reporting system that characterizes mutations as pathogenic, likely pathogenic, benign, likely benign, or a variant of unknown or uncertain significance (VUS).[48] To increase the accuracy of these assignments, there has been an emphasis on data sharing to help determine whether the identified genetic variant has ever been encountered, and if so, whether it was associated with a clinical phenotype. Toward that end, the National Center for Biotechnology Information of the US National Institutes of Health (NIH) has established a database of genetic variants and associated clinical phenotypes, ClinVar, that serves as a resource for healthcare providers and genetic testing services. Depending on the type of variant observed (eg, a sequence variant or insertion/deletion variant), other databases such as dbSNP, dbVar, ExAC, and 1000 Genomes can be used to determine whether the variant has been observed in previously sequenced population cohorts (Table 5). However, one should be aware that these healthy control databases include pathogenic variants, and this should be considered when studying low-penetrance or late-onset phenotypes. A particular variant can be reclassified into a different pathogenic category (eg, a pathogenic variant or VUS might be classified as benign in the future as more evidence becomes available). ClinGen is a data-sharing portal that provides genotype-phenotype data and thereby serves as a resource for identification of clinically relevant variants to clinicians, researchers, and even patients.[49] There is also a risk for false-positive results (ie, variants that are benign or VUS could be misclassified as disease causing). As discussed further in Variants of Unknown Significance, the likelihood

Table 4. Diagnostic Yield of Commonly Used Cardiac Genetic Tests

Test	Methodology	Diagnostic Yield
Cardiomyopathy, arrhythmogenic right ventricular	Sequencing	40%–60%
Cardiomyopathy, dilated	Sequencing	20%–30%
Cardiomyopathy, hypertrophic	Sequencing	30%–50%*
Channelopathy, Brugada syndrome	Sequencing	25%–30%
Channelopathy, catecholaminergic polymorphic ventricular tachycardia	Sequencing	55%–65%
Channelopathy, long-QT syndrome	Sequencing	70%–75%
Congenital heart disease, nonsyndromic	Sequencing and/or chromosome microarray	3%–10%
Congenital heart disease, syndromic	Sequencing and/or chromosome microarray	25%–35%
Familial hypercholesterolemia	Sequencing	60%–80%
Familial thoracic aortic aneurysm and dissection	Sequencing	25%
Marfan syndrome	Sequencing and deletion/duplication	90%–95%

*The detection rate was 30% in unselected probands and 50% or higher in familial cases.[45]

Table 5. Examples of Publicly Available Genetics Resources and Databases

Resource or Database	Description
ClinGen http://www.clinicalgenome.org	Portal for data sharing to speed the identification of clinically relevant variants
ClinVar http://www.ncbi.nlm.nih.gov/clinvar	Database of interpretation about genotype-phenotype relationship of human variation in disease
dbSNP http://www.ncbi.nlm.nih.gov/snp	NCBI public archive of genetic variation across various species
dbVAR http://www.ncbi.nlm.nih.gov/dbvar	NCBI database of genomic structural variation
Exome variant server http://evs.gs.washington.edu/EVS/	Database of exome sequencing data from individuals sequenced through the NHLBI GO Exome Sequencing Project (ESP)
ExAC browser http://exac.broadinstitute.org/	Database of exome sequencing data from unrelated individuals from a variety of large-scale sequencing projects
GeneReviews http://www.ncbi.nlm.nih.gov/books/NBK1116/	Expert-authored, peer-reviewed disease descriptions focused on clinically relevant and medically actionable information on the diagnosis, management, and genetic counseling of patients and families with specific inherited conditions
Human Gene Mutation Database http://www.hgmd.org	Database of variant annotations in disease published in the literature; requires subscription
Human Genome Variation Society http://www.hgvs.org	Database with variant annotations on specific subsets of human variation in disease
OMIM http://www.omim.org	Database of human genes and genetic conditions in disease
POSSUMweb http://www.possum.net.au	Database of dysmorphology, including multiple malformations, metabolic, teratogenic, chromosomal and skeletal syndromes and their images; requires subscription
RefSeqGene http://www.ncbi.nlm.nih.gov/refseq	Database of medically relevant gene reference sequence
1000 Genomes http://www.1000genomes.org	Database of genomic variants derived from next-generation sequencing of healthy control subjects

dbSNP indicates Database of Single Nucleotide Polymorphisms; dbVAR, Database of Genomic Structural Variation; ExAC, Exome Aggregation Consortium; NCBI, National Center for Biotechnology Information; NHLBI, National Heart, Lung, and Blood Institute; OMIM, Online Mendelian Inheritance in Man; POSSUM, Pictures of Standard Syndromes and Undiagnosed Malformations.

of this scenario is increased when the proband has an unclear clinical diagnosis or phenotype or when a testing panel with a large number of genes is sent (which statistically increases the likelihood of finding a rare variant). This emphasizes the importance of selecting the best genetic test and testing the most clearly affected family member whenever possible. Misclassification can not only cause a wrong diagnosis in an affected person but can result in the classification of a mutation-negative family member as healthy because they lack what is thought to be a disease-causing variant. It is therefore critical that genetic testing laboratories notify clinicians of any updates to variant classification so that screening and management decisions for the patient and their family can be modified appropriately.

Variants of Unknown Significance

As might be expected, the most difficult category to use clinically is the VUS. This designation indicates that there is insufficient data or conflicting data regarding the mutation, which prevents its assignment as either benign or pathogenic. Laboratories can differ in their interpretation of the pathogenicity of variants, and the ACMG has proposed guidelines for a standardized approach to the classification of the pathogenicity of variants.[48] By definition, a VUS should not be used for clinical decision making because it represents an indeterminate result. In some cases, practitioners can aid in the correct classification by identifying other family members with the condition and determining whether the variant segregates with disease. This process is nuanced and should be disease and family specific. Genetic testing is probabilistic, and VUSs neither support nor refute an underlying genetic pathogenesis. Pretest counseling of the family can appropriately prepare them for a potentially uncertain result. It is important to recognize that VUSs can be reclassified over time, as their status changes from uncertain to likely pathogenic or likely benign, and patient and family risk should be readdressed at that time. A particularly problematic scenario is the one in which the genetic test is being used to help establish a clinical diagnosis. The pretest probability of a positive, negative, or uncertain result is important to consider in the context of the clinical presentation and family history and will vary by specific disease process and available genetic testing. Maximizing the testing yield while minimizing VUS results should be an objective that influences test choice, especially in scenarios of unclear clinical diagnoses. In these situations of unclear clinical phenotypes, it is especially important that care providers resist the temptation to act on uncertain genetic test results. Genetic test results with VUS findings are continuing to rise as (1) genetic testing becomes more widely used for an increasing number of conditions; (2) gene panels for specific cardiovascular conditions evaluate an increasing number of genes to include newly identified, rare causes of the condition (often very little is known about these newer disease genes, which means that most variants in those genes will be classified as VUSs); and (3) there is increased utilization of nondirected tests (such as clinical exome and genome sequencing) that will uncover a large number of VUSs in patients who often lack a clearly defined clinical diagnosis. As genetic testing continues to expand, careful consideration needs to be given to determining who needs to be tested and what is the most appropriate test given the cardiac phenotype, as well as to ensuring that the patient and family have been counseled appropriately regarding the possible outcomes and consequences of the test.

Predictive Testing

Once a mutation has been identified and determined to be responsible for a disease phenotype, other family members can be tested to determine whether they have inherited that particular mutation. The most direct benefit of performing "cascade" genetic testing of other family members is the presymptomatic identification of people at risk for developing the condition. This is relevant only for those conditions in which presymptomatic treatment can prompt interventions that delay disease onset, reduce disease severity, prevent a sudden catastrophic event, or influence reproductive counseling. For all conditions that could develop with time or for which the establishment of a clinical diagnosis is challenging, genetic testing of unaffected family members can determine who is and is not at risk for developing the condition, which allows for careful monitoring of presymptomatic people and provides reassurance (and obviates the need for continued screening and monitoring) in those people determined not to be at risk.

Retesting or Expanded Testing

When genetic testing does not identify a causal mutation in a patient with a cardiovascular condition, it is important to consider the type and extent of testing performed. A test that includes more or different genes or one that includes testing for additional types of mutations, such as copy number variation, might be required. If the test was performed in the past and did not yield a definitive result, then the test can be repeated as more causal genes are identified and expanded panels are developed. If multiple family members with a specific condition are identified but directed genetic testing has not identified a causal genetic variant, then clinical exome or genome sequencing can be performed. Similarly, exome or genome sequencing of a parent-child trio can be helpful in identifying a novel de novo mutation in a child with a severe cardiovascular phenotype but no family history of the condition.[50]

Secondary Findings

Nontargeted tests such as clinical exome or genome sequencing carry a finite likelihood of uncovering genetic variants that might have important medical implications for the patient and the patient's family but might not be related to the primary medical condition for which the testing was performed. These secondary or incidental findings might be important to identify and act on to preserve the health of the patient. However, what constitutes an actionable genetic variant (a genetic variant that a provider is obligated to communicate to the patient and family) remains controversial. The ACMG recommended that a known or expected pathogenic variant in 1 of 56 target genes should be communicated to the family (Table 6).[51] Importantly, of the 56 genes, 28 are associated with cardiovascular conditions such as Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome (type IV), hypertrophic cardiomyopathy, dilated cardiomyopathy, catecholaminergic polymorphic ventricular tachycardia, arrhythmogenic right ventricular cardiomyopathy, LQTS, and Brugada syndrome.

As this type of testing becomes more widespread, there could be an increasing number of patients referred for cardiovascular evaluation who have been informed that they are at risk for a cardiovascular condition based on receiving actionable results from genetic testing. If the testing was performed in a research laboratory, confirmation of findings in a Clinical Laboratory Improvement Amendments–certified laboratory is required. For many of these conditions, variability in disease onset and incomplete penetrance will present an important clinical challenge in determining the significance of the identified genetic abnormality. A careful and detailed family history, clinical testing (including provocative testing or serial testing if appropriate), and familial segregation analysis might be required to determine whether the patient has or is at risk for developing a cardiovascular condition. This requires close coordination between the geneticist and the cardiovascular specialist.

Table 6. American College of Medical Genetics and Genomics List of Genes Associated With Cardiac Disorders in Which Mutations Are Reportable

Condition	Gene
Arrhythmogenic right ventricular cardiomyopathy	*PKP2, DSP, DSC2, TMEM43, DSG2*
Cardiomyopathy, hypertrophic or dilated	*MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL3, ACTC1, PRKAG2, GLA, MYL2, LMNA*
Catecholaminergic polymorphic ventricular tachycardia	*RYR2*
Ehlers-Danlos syndrome (vascular type)	*COL3A1*
Familial hypercholesterolemia	*LDLR, APOB, PCSK9*
Long-QT syndromes 1, 2, and 3	*KCNQ1, KCNH2, SCN5A*
Marfan syndrome, Loeys-Dietz syndrome, and familial thoracic aortic aneurysms and dissections	*FBN1, TGFBR1, TGFBR2, SMAD3, ACTA2, MYLK, MYH11*
Tuberous sclerosis syndrome	*TSC1, TSC2*

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Impact of Genetic Test Results

Before ordering genetic testing, it is important to have a clear understanding of the impact of the results on the patient and the patient's family. The highest level of evidence for genetic testing exists for those conditions in which the results will directly impact the care of the patient or family. For instance, the timing of surgical intervention for patients with ascending aortic aneurysms can depend in part on the genetic defect responsible for the condition.[28,52] For example, patients with Loeys-Dietz syndrome and aortic root dilatation might require surgical intervention sooner (ie, at a lesser degree of dilation) than patients with Marfan syndrome or other causes of root dilation.[53] Similarly, the presence of a truncating mutation in lamin A/C (*LMNA*) in a patient with Emery-Dreifuss muscular dystrophy is a risk factor for SCD and is an important component of the algorithm for determining whether placement of an implantable cardioverter-defibrillator is indicated for primary prevention.[54] A genetic diagnosis might also make the patient eligible for clinical trials related to the condition (a list

Table 7. Genetics-Guided Diagnosis and Management of Cardiovascular Conditions

Condition	Role in Diagnosis	Role in Management	Citation(s)
Aortopathies			
Familial thoracic aortic aneurysm and dissection	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	Hiratzka et al[26]
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	MacCarrick et al[53]
Marfan syndrome	Major criterion for diagnosis	Confirmed diagnosis can affect (1) timing of recommended surgical intervention and (2) extent and type of screening for other abnormalities	Radke et al[52]
Rhythm disorders			
Brugada syndrome	Can support clinical diagnosis	Aids with identification of family members at risk for the condition	Schwartz et al[32] Ackerman et al[16]
Catecholaminergic polymorphic ventricular tachycardia	Major criterion for diagnosis and subtype classification	Aids with identification of family members at risk for the condition	Schwartz et al[32] Ackerman et al[16]
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	Schwartz et al[32,56] Guidicessi et al[57] Barsheshet et al[58] Ackerman et al[16]
Cardiomyopathies			
Arrhythmogenic right ventricular cardiomyopathy	Major criterion for diagnosis and subtype classification	Aids with identification of family members at risk for the condition	Pinamonti et al[59] Marcus et al[60]
Hypertrophic/dilated cardiomyopathy	Can support clinical diagnosis and subtype classification	Aids with identification of family members at risk for the condition; informs how and when family members should be screened based on genotype status	Ho et al[61] Hershberger et al[17]
RASopathy syndromes	Confirm clinical diagnosis and subtype classification	Causative gene can affect extent and type of screening for other abnormalities	Rauen[62]
Neuromuscular disorders			
Duchenne/Becker muscular dystrophy	Major criterion for diagnosis	Certain types of mutations can be specifically targeted using experimental treatments	Touznik et al[63]
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)	Beynon et al[64] Wang et al[65]
Emery-Dreifuss muscular dystrophy	Major criterion for diagnosis and subtype classification	Type of mutation (missense vs. truncating) is important for determining risk of sudden death and need for ICD placement for primary prevention	van Rijsingen et al[54]
Friedreich ataxia	Confirm clinical diagnosis	Trinucleotide repeat size correlates with severity and age of onset; aids with identification of family members at risk for the condition	Corben et al[66]

ICD indicates implantable cardioverter-defibrillator.

of which can be found on the ClinicalTrials.gov registry[55]). A summary of cardiovascular conditions for which genetic test results can impact diagnosis or management is presented in Table 7.[1,17,26,32,52–54,56–66]

For some conditions, a positive genetic test is an important part of establishing the diagnosis.[28,67] This can be particularly useful in cases in which the clinical tests are indeterminate and for conditions in which clinical tests lack sensitivity or specificity. However, there are some important implications of performing genetic testing in people who have not yet demonstrated any evidence of a cardiovascular condition based on clinical evaluation, and these should be clearly discussed with the patient before genetic testing is performed.[68] It could also impact the person's ability to acquire some types of insurance. To protect the rights of patients who have had genetic testing, the US Congress passed the Genetic Information Nondiscrimination Act (GINA) in 2008. The Genetic Information Nondiscrimination Act is designed to prohibit discrimination through the use of genetic information in health insurance and employment.[69] However, it does not prohibit the use of genetic test results by companies offering life insurance or long-term care policies, which might be able

to use that information to deny coverage or raise premiums.[70] It is therefore important that genetic testing be offered in the context of appropriate genetic counseling, so that insurance and other risks are fully discussed beforehand and the family is provided an opportunity to acquire appropriate insurance coverage before testing.

Cardiovascular practitioners should be aware that although guidelines for interpretation of genetic testing results exist, interpretations can vary among laboratories.[48,71,72] Importantly, practitioners also need to be aware that classification of variants can change over time as new information emerges, and this information should be revisited. Centers with high volumes of patients and genetic testing typically have established practices for reviewing test reports, partnering with testing laboratories and local geneticists and genetic counselors, and updating or altering test summaries based on their independent reinterpretation.[73] Similarly, family history is dynamic and should be updated over time. This is time intensive but directly impacts family-based recommendations and care. Incorporation of genetic testing information requires a paradigm shift from a model of treating the individual to family-based care, and practitioners should be aware of guidelines and recommendations for cardiovascular evaluation and genetic testing in first-degree relatives of affected individuals.[16,17,26] Specific areas of knowledge are discussed in the following sections.

In summary, genetic testing can have an important impact on establishing a diagnosis, identifying who is (and who is not) at risk for developing a particular cardiovascular condition, and directing appropriate clinical care. The specific benefits vary by condition, and it is important to understand the implications of testing and to work with patients and families to determine how the results will be used.

When Do I Use Pharmacogenetic Testing?

The expanding field of pharmacogenetics, which refers to genetic influences on drug response, is another area about which cardiovascular practitioners should have a basic working knowledge, because they will often be required to order a pharmacogenetic test before initiating a drug that carries a pharmacogenetic label, without referral to a genetics professional. Although widespread and routine use of genetic information in cardiovascular medication selection is not yet the standard, the field has advanced considerably toward clinical utility. There are specific drugs for which pharmacogenetic variant information can be reasonably used today, and this has become part of routine care at early adopter centers. A common philosophy in such centers is that genetic variant data can be viewed like physiological data or other biomarkers (eg, of renal or liver function) that have an impact on drug effects. For cardiovascular practice today, a few general principles and specific areas of knowledge are suggested. To date, the use of genetic variant data in clinical drug use has been confined to relatively common variants with large effect sizes (especially in homozygote or compound heterozygote variant carriers). Future applications will turn to rarer sequence variants and the use of variant data to identify potential new drug targets, such as *PCSK9*, *APOC3*, or *SLC30A8*.[74–76]

The overarching principle in pharmacogenetics is to identify genetic determinants that affect drug response and therefore can help in selecting the best therapies or dosages for particular subsets of patients based on genotype. Pharmacokinetic variants have an impact on drug transport or metabolizing enzymes, thereby affecting the relative drug exposure, dosing, and interactions (eg, *SLCO1B1* and simvastatin, or *CYP2D6* and a range of substrates including flecainide, propafenone, and many β-blockers).[77] Alternatively, genetic variants can act by pharmacodynamic mechanisms on drug targets rather than drug exposure (eg, effector receptors or downstream pathways such as *ADRB1* and bucindolol).[78,79]

Along with understanding the general principles, methods of maintaining up-to-date knowledge are critical. There are numerous review articles summarizing the state of cardiovascular pharmacogenomics.[80–82] In terms of specific drug-gene interactions, the US Food and Drug Administration (FDA) website lists all FDA-labeled drug-gene interactions, which can be a useful compendium.[83] At the time of this writing, there were 158 specific labels, of which 16 were cardiovascular related (excerpted in Table 8). In terms of updated reference material, the Pharmacogenomics Knowledgebase[84]

Table 8. FDA Labeling of Pharmacogenetic Interactions Involving Cardiovascular Drugs[83]

Drug	Pharmacogene	Phenotype
Carvedilol	*CYP2D6*	CYP2D6 poor metabolizers/ultrarapid metabolizers
Clopidogrel	*CYP2C19*	CYP2C19 intermediate or poor metabolizers
Flecainide	*CYP2D6*	CYP2D6 poor metabolizers/ultrarapid metabolizers
Isosorbide and Hydralazine	*NAT1-2*	Slow acetylators
Metoprolol	*CYP2D6*	CYP2D6 poor metabolizers/ultrarapid metabolizers
Mexiletine	*CYP2D6*	CYP2D6 poor metabolizers/ultrarapid metabolizers
Prasugrel	*CYP2C19*	CYP2C19 poor metabolizers
	CYP2C9	CYP2C9 variant carriers
	CYP3A5	CYP3A5 variant carriers
	CYP2B6	CYP2B6 variant carriers
Propafenone	*CYP2D6*	CYP2D6 poor metabolizers/ultrarapid metabolizers
Propranolol	*CYP2D6*	CYP2D6 poor metabolizers/ultrarapid metabolizers
Quinidine	*CYP2D6*	CYP2D6 poor metabolizers/ultrarapid metabolizers
Ticagrelor	*CYP2C19*	CYP2C19 poor metabolizers
Warfarin	*CYP2C9*	CYP2C9 intermediate or poor metabolizers
	VKORC1	VKORC1 A allele carriers
	PROS	Protein S deficient
	PROC	Protein C deficient

is an online repository that curates information on all pharmacogenetic interactions, including both research data and clinical decision guides and dosing algorithms.[85] The Clinical Pharmacogenetics Implementation Consortium publishes guidelines for implementation of pharmacogenetic test results into clinical practice and actionable prescribing decisions, with prioritization of tests offered in Clinical Laboratory Improvement Amendments–approved laboratories. Notably, the Clinical Pharmacogenetics Implementation Consortium guidelines center around how to apply a pharmacogenetic test result, not around whether and when to order the test.[86] Warfarin and clopidogrel are 2 better known examples of drugs used commonly in heart disease patients that have FDA pharmacogenetic labeling to guide choice and dose of drug. The FDA recommends companion testing for variants in *VKORC1* and *CYP2C9* and adjustment of warfarin starting dose by genotype to improve time in therapeutic international normalized ratio range based on several studies and trials.[87–92] The FDA also recommends avoiding clopidogrel in patients with loss-of-function variants in *CYP2C19*, although trials have reported mixed results with benefits of a genotype-guided approach.[93–98]

Therefore, it is important for the clinician to keep up-to-date with emerging pharmacogenetic labeling to ensure that recommended guidelines surrounding genotype-guided drug dosing or choice are followed appropriately. Eventually, electronic health records could enable incorporation of decision algorithms at the point of care to permit the practitioner to practice genotype-guided drug prescribing.

What Do I Need to Know About Emerging Genetic and Genomic Technologies?

The rapid pace of innovation in DNA sequencing technologies and new approaches to gene therapy make for an exciting future for the diagnosis and treatment of cardiovascular diseases, and it is important that the cardiovascular practitioner keep abreast of these advancements as they relate to personalized or precision medicine, especially as patients and families become active and vocal participants in their own care. The decline in genotyping and sequencing costs over the past 20 years has allowed for new discoveries in the genetic basis of cardiovascular disorders and for the expanded use of genetic testing in patients with undiagnosed cardiovascular conditions. The cardiovascular practitioner should have sufficient knowledge of the current evidence base and state of the art in genetic and genomic technologies relevant to clinical care to enable them to feel comfortable addressing patient queries. Here, we summarize the emerging technologies in the field of cardiovascular genetics of which a clinician should be aware and provide a framework for keeping abreast of advances as the field continues to progress.

Next-Generation Sequencing in Clinical Diagnostics

The precipitous drop in DNA sequencing costs is the result of next-generation sequencing techniques. Next-generation sequencing techniques are able to sequence many DNA strands in parallel and thus determine the identity of up to billions of DNA bases in a matter of hours.[99] Many companies offer next-generation sequencing platforms for clinical genetic testing. There is still considerable variability in the sensitivity of detection of single-nucleotide variants depending on comprehensiveness of sequence capture and depth of sequencing, as well as discordance in variant calls between laboratories. In addition, there are high false-positive and false-negative rates for insertions, deletions, inversions, duplications, and more complex rearrangements.[100] Methods in development are poised to solve these problems by sequencing longer DNA strands. The declining costs and increasing coverage could soon make clinical genome sequencing a reasonable alternative to clinical exome sequencing and perhaps even gene panels. This has been demonstrated for cardiomyopathy-related genetic testing, in which 30 to 40× coverage by whole-genome sequencing accurately identified known mutations.[101] However, next-generation sequencing also increases the likelihood of detecting VUSs, especially the uncertain functional significance of noncoding variants identified with genome sequencing. A joint statement by the European Society of Cardiology and European Society of Human Genetics proposed a conservative approach to the use of next-generation sequencing in genetic diagnosis of hereditary cardiovascular conditions.[102]

Noninvasive Prenatal Genetic Testing

One immediate clinical application of next-generation sequencing has been the early diagnosis of fetal trisomies by use of cell-free DNA in the maternal circulation.[103] The recent extension of this technique to all women in a prospective randomized trial found superior specificity and sensitivity for all 3 trisomies studied compared with standard nongenetic prenatal screening.[104] Current screening for heart disease in the fetus is limited to fetal echocardiography in high-risk pregnancies, but this can only be done in the mid-late second trimester. As the technology for cell-free DNA sequencing expands to include the detection of smaller genetic aberrations, many of which are associated with CHDs,[105] these tests might be offered in the future to identify fetuses who are genetically at risk for cardiac disease sooner than would be detected by fetal cardiac imaging. This can facilitate earlier confirmatory testing and early interventions if indicated.

Genetic Testing for Common Variants

Genome-wide association studies have identified regions of association in large studies of atrial fibrillation, coronary artery disease, myocardial infarction, lipid traits, hypertension, and quantitative traits such as the QT interval.[106] For coronary artery disease, there are now at least 46 loci with genome-wide significant associations.[107] The vast majority of genome-wide association study loci confer a very modest effect size on disease risk. Aggregation of loci into genetic risk scores is being increasingly explored as a way to improve predictive ability for disease, as well as modifiers of disease phenotype, although this approach requires further validation.[108–112] Direct-to-consumer testing companies offer testing for variants associated with many common diseases, including cardiovascular diseases. The FDA issued a warning in 2013 prohibiting companies from providing direct health information to US consumers without FDA approval of the accuracy, reliability, and clinical utility of their tests. The FDA has since authorized marketing of a direct-to-consumer genetic test aimed at detecting the carrier status for a serious disorder that a healthy person can transmit to their offspring. The healthcare provider should therefore be aware of the changing landscape of approved direct-to-consumer testing that could lead

to patients and families seeking medical opinions based on results of such testing.

Gene Therapy for Cardiovascular Disorders

The therapeutic relevance of understanding the genetic basis of cardiovascular disorders is now reemerging in the form of gene therapy. This can involve replacing a mutated gene that causes disease with a healthy copy of the gene, inactivating a mutated gene that is functioning improperly, or introducing a new gene into the body to treat a disease. Although there is excitement in the field over emerging uses of gene therapy for cardiovascular disorders, safety and efficacy are still being intensely explored.

Gene therapy for the modulation of cardiac contractility by increasing cardiac myocyte Ca^{2+} flux is moving forward on 2 fronts. First, the adeno-associated virus–mediated delivery of sarcoplasmic reticulum Ca^{2+}-ATPase to patients with cardiomyopathy was tested in the CUPID trial (Calcium Up-Regulation by Percutaneous Administration of Gene Therapy in Cardiac Disease). Despite promising early results with the CUPID trial,[113] the subsequent CUPID-2 trial failed to show an improvement in clinical outcomes.[114] Efforts are under way to use adeno-associated virus–mediated delivery of S100A1, a Ca^{2+} binding protein, to reduce intracellular calcium sequestration.[115,116] The first human trial of adeno-associated virus–mediated delivery of S100A1 therapy is expected to start in 2016.

Genome Editing

Genome editing is a rapidly expanding field that entails the use of artificially engineered nucleases designed with sequence-specific DNA-binding domains. Rapid progress in the development of genome-editing platforms has led to the demonstration of highly efficient and precise therapy in preclinical models. Investigators have shown an ability to introduce a variety of genetic alterations into mammalian cells, ranging from knock-in of single-nucleotide variants to insertion of genes and chromosomal regions. An accounting of the discovery of the various genome editing systems is beyond the scope of this statement, although it makes for a fascinating demonstration of the translation of basic scientific research on bacteria and plants to the study and eventual treatment of human diseases.[117] There are already promising applications of genome editing in hematologic disorders, most notably HIV infection.[118] An early demonstration of genome editing relevant to cardiovascular disease was the permanent disruption of the *PCSK9* gene in mice, which resulted in substantial reduction of blood cholesterol levels,[119] an approach that could eventually translate into a 1-shot "vaccine" for coronary artery disease. Although more technically challenging, the ability to correct missense mutations that are causal for disease raises the intriguing possibility of treating a variety of cardiovascular conditions, such as inherited forms of cardiomyopathy and LQTS.

The emerging technologies described here are advancing at remarkable speed with growing academic-industry partnerships to promote application of genetics to gene therapy, risk-prediction methods, and more efficient sequencing technologies, including point-of-care sequencing tests. The recently announced Precision Medicine Initiative by the NIH provides funding and a website[120] where advances will be chronicled.[121] The cardiovascular practitioner needs to stay abreast of these advances as they enter the mainstream.

How to Acquire and Maintain Genetics Competencies

As new genetics and genomics knowledge continues to become integrated into health care, it will be essential to ensure that practitioners acquire and maintain the necessary competencies to guide the continuum of care along the pathways of prevention, screening, monitoring, diagnostics, prognostics, treatments, and counseling. The Institute of Medicine recently held a workshop focused on "Improving Genetics Education in Graduate and Continuing Health Professional Education." The objectives of the Institute of Medicine workshop were to (1) examine the potential and the challenges of providing genetics education; (2) review promising and innovative approaches to providing education to both graduate health professional students and practicing health professionals; and (3) identify potential next steps for achieving effective genetics education. Two critical next steps identified were to (1) increase the genetics/genomics IQ of healthcare providers and (2) ensure the genetics and genomics literacy of a diverse team of healthcare providers. With the recent announcement by the White House of an investment in precision medicine, the ACMG has actively begun the development of practice guidelines for clinicians and laboratories and has partnered with the ClinGen Project to bring together expertise in the field of genetics and genomics to prepare for a new era of genomic health care.[49,122]

The NIH's National Human Genome Research Institute (NHGRI) formed the Inter-Society Coordinating Committee for Practitioner Education in Genomics in February 2013 to facilitate interactions among more than 2 dozen medical professional societies and the various NIH institutes and centers and to exchange practices and resources in genomics education and clinical care.[123] The Inter-Society Coordinating Committee for Practitioner Education in Genomics has been working to (1) develop clinical competencies, (2) collect and disseminate genetics and genomics case studies, (3) collect and disseminate educational products, (4) engage with specialty boards to foster the integration of genetics and genomics into board examinations, (5) provide education for the staff of health insurers, (6) create recommendations for language used by practitioners in communicating genetics and genomics concepts to patients, and (7) develop innovative methods of teaching genetics and genomics to practitioners (eg, a "flipped classroom" model in which practitioners learn from online materials in combination with participation in special workshops at professional society conferences).

Many professional societies have individually released or revised practice competency standards or policies focused on genetics and genomics to meet the needs of their specialties, including the American Academy of Family Physicians, the American Medical Association, the American Academy of Pediatrics Committee on Genetics, the American Society of Clinical Oncology, and the ACMG.[5,38,124–129] The creation of an international certification for genetically trained nurses and nurse practitioners through the American Nurses Credentialing Center in 2015 will provide genetic training within nursing specialties.

Table 9. Resources Available to Healthcare Professionals to Enhance Knowledge of Genetics and Genomics

Entity	Description
American Academy of Pediatrics Genetic Literacy in Primary Care Colloquium	An initiative of the Genetics in Primary Care Institute that has published articles related to delivery of genetic services in daily pediatric primary care practice, along the spectrum of prevention, diagnosis, and management, as well as family history tools (https://geneticsinprimarycare.aap.org/Pages/default.aspx).[121,122,124]
American Medical Association Genetics and Genomics Competency Center	A free online collection of genomics education materials for use in teaching and self-learning for physicians, genetic counselors, nurses, pharmacists and physician assistants developed by the NHGRI. Formats include webinars, glossaries, fact sheets, guides, and self-study activities including opportunities for CME credits (http://g-2-c-2.org).
American Nurses Credentialing Center (ANCC)	The ANCC in 2015 created an international certification for genetic nursing. Through a portfolio process, candidates seeking certification are required to meet certain eligibility and practice requirements for genetic nursing in their specialty area. The portfolio application is evaluated and scored by expert genetic nurse appraisers for specific evidence of elements related to genetics/genomics are meet. Successful candidates are awarded board certification, which is renewed every 5 y.
G3C Global Genetics and Genomics Community	A bilingual collection of unfolding case studies that can be used with healthcare providers and students to understand basic genetics and genomics concepts and their application to practice (http://g-3-c.org/en).
Genetics and Common Disorders: Implications for Primary Care and Public Health Providers	A program being offered free to physicians and other healthcare professionals on a CD-ROM (http://www.ama-assn.org/ama/pub/physician-resources/medical-science/genetics-molecular-medicine/education-research.page).
Institute of Medicine workshop on genetic education	Published a workshop summary on improving genetics education in graduate and continuing health profession education (http://iom.nationalacademies.org/Reports/2015/Improving-Genetics-Education-Graduate-Continuing-Health-Professional-Education.aspx).
National Coalition for Health Professional Education in Genetics (NCHPEG)	Founded in 1996 by the American Medical Association, the American Nurses Association, and the NHGRI to promote health professional education and access to information about advances in human genetics. The coalition has developed consensus core competencies in genetics, educational resources on topics relating to clinical genetics, and a search engine to provide health professionals and the public with high quality information related to human genetics, with a particular focus on genetic medicine and health (http://www.nchpeg.org/).

CME indicates continuing medical education; and NHGRI, National Human Genome Research Institute.

The US Secretary for Health and Human Services Advisory Committee on Heritable Disorders in Newborns and Children has provided recommendations for incorporation of genetics and genomic medicine education for primary care physicians in maternal and child health.[130] Additionally, the American Heart Association has published several policy statements and guidelines for application of genetics to the care of children and adults with heart disease.[20,131–133] These efforts provide resources to guide incorporation of genetics and genomics into the practice of cardiovascular health care. Several general and specialty-specific resources available to practitioners are listed in Table 9.

Table 10. Enhancing Genetic Knowledge of Cardiovascular Healthcare Professionals

Incorporate case-based genetics and genomic medicine educational curriculum involving common genetic concepts in fellowship training programs
Assess basic literacy in genetics and genomic medicine in board certification and maintenance of certification
Incorporate cardiovascular genetics and genomics content into continuing medical education
Develop and disseminate genetic evidence-based guidelines for care of patients with heart disease
Point-of-care and Internet-based tools for clinical decision support surrounding application of genetics and genomics towards diagnosis and management of cardiovascular disorders

Additionally, there are training and certification programs available at different levels besides those offered by the American Board of Medical Genetics and Genomics in the form of studentships, fellowships, workshops, online courses, case-based learning, and laboratory courses. These include National Heart, Lung, and Blood Institute training programs, the National Institute of Nursing Research Summer Genetics Institute, the NIH Undiagnosed Diseases Program, NHGRI medical genetics residency and fellowship training programs, the NHGRI Physician Scientist Development Program, the NHGRI Combined Pediatrics and Medical Genetics Residency Program, the NIH Post-Baccalaureate Intramural Research Training Award, and the Johns Hopkins University/NHGRI Genetic Counseling Training Program.

In addition to formal training programs, online resources exist for genetic diseases, genetic variation, and cytogenetic and molecular testing. There are extensive resources for computational and predictive data related to variant classification, although interpretation of VUSs becomes a growing challenge as genetic testing is more widely adopted.[48] In addition, there are a number of online resources available for families that are diagnosis specific and that explain the genetic basis of disease and, when relevant, the implications for family members. Table 5 lists common online resources used for genetic information. More comprehensive lists are available in recent guidelines and reviews.[37,48,134,135] Details of available clinical genetic tests can be found on the GeneTests website.[136] Table 10 lists additional strategies for incorporating ongoing genetics/genomics learning into clinical cardiovascular practice.

Conclusions

This is an exciting time in the field of medicine, when the application of genetics and genomics-driven diagnostics, prognostics, and therapeutics is seeing a rapid growth. The federal investment in the Precision Medicine Initiative has energized the field of genomic applications in health care. The

applications to cardiovascular diseases and stroke are expected to see similar growth, and the cardiovascular clinician needs to be well informed about this burgeoning field and how to effectively apply it to the care of their patients. This statement provides the current and future state of knowledge in which the clinician needs to be proficient, the public resources available to the clinician to stay abreast of this knowledge, recommendations for increasing genetic awareness and education among practicing clinicians, and the importance of close collaboration with genetics specialists. Societies such as the American Heart Association should invest in educational tools and resources to increase genetics awareness and knowledge through continuing medical education. This can be achieved through collaboration with the ACMG on certification programs for cardiovascular geneticists and by increasing genetics content on maintenance-of-certification programs for cardiologists and cardiovascular specialists. The eventual goal is to empower and enable the cardiovascular clinician to understand, interpret, and apply genetic information to patient care in an effective, responsible, and cost-efficient manner.

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Caroline Fox is currently employed by Merck and was employed by the NHLBI during the development of this manuscript. Kiran Musunuru is currently employed by the University of Pennsylvania Cardiovascular Institute and was employed by Harvard University during the development of this manuscript.

*Modest.

†Significant.

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*Modest.

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Enhancing Literacy in Cardiovascular Genetics: A Scientific Statement From the American Heart Association

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on behalf of the American Heart Association Council on Functional Genomics and Translational Biology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Stroke Council; Council on Lifestyle and Cardiometabolic Health; and Council on Quality of Care and Outcomes Research

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Supplemental Table 1: Basic human genetics terminology

Terminology	Description
Allele	Alternative version of a genetic sequence at a particular locus
Aneuploidy	Having an abnormal number of chromosomes
Benign variant	A variant which does not have a deleterious impact on gene function
Cytogenetics	Analysis of number and structure of chromosomes
Dominant	Gene alteration producing a phenotype when expressed in a heterozygous state
Fluorescence In-Situ Hybridization (FISH)	Fluorescent DNA probes attach (hybridize) to specific sequence if present; can be done rapidly and detects submicroscopic deletions/duplications, resolution ~35kb
Genotype	Genetic make-up of an individual, specifically a set of alleles that determines expression of a particular trait
Heterozygous	Having different alleles at a given locus
Homozygous	Having the same allele at a given locus
Karyotype	Profile of all of an individual's chromosomes
Linkage	Genes within a measurable distance of each other that are normally inherited together
Locus	Location of a gene or marker on the chromosome
Microarray	Hybridization technique using thousands of probes to assess dosage of multiple areas of the genome simultaneously to look for submicroscopic copy number variants (CNVs) either deletions or duplications
Mutation	Variation in DNA sequence (e.g. substitution, deletion, insertion) often at a single base pair, usually used in the context of a polymorphism that is rare (occurs in less than 1% of the population) and potentially pathogenic
Non synonymous variant	Alters the amino acid sequence of encoded protein

Supplemental Table 1 (continued)

Insertion / deletion	Addition or loss of one or more nucleotides
Missense variant	Nucleotide substitution that results in a codon that codes for a different amino acid
Nonsense variant	Nucleotide substitution that results in a premature stop codon causing a truncated, non-functional protein
Splice site variant	Alters nucleotides at splice sites resulting in abnormal protein
(Gene) Panel testing	Sequencing of a panel of genes associated with a phenotype or overlapping phenotypes
Pathogenic variant	A variant considered to be disease causing by the laboratory based on several criteria including the type of variant, functional studies, rarity in ethnicity-matched control populations, conservation among species and segregation with disease or de novo inheritance
Pedigree	A diagram representing a family tree
Polymorphism	Variation in DNA sequence (e.g. substitution, deletion, insertion) often at a single base pair (90% of all human genetic variation)
Proband	First affected individual in a family (also known as index case)
Rare variant	Variation in DNA sequence that occurs in less than 1% of the population
Recessive	Gene alteration producing a phenotype only when expressed in homozygous state
Single nucleotide substitution	Replacement of one nucleotide with another
Splicing	Process by which introns are removed and exons are joined in pre-mRNA transcript
Synonymous variant	DNA sequence variant that does not alter the amino acid sequence of encoded protein
Transcription	Synthesis of a RNA from a DNA segment as a first step in gene expression

Supplemental Table 1 (continued)

Translation	Generation of protein from a sequence of messenger RNA
Variant of unknown significance (VUS)	A variant where there is insufficient evidence for the laboratory to classify it as either benign or pathogenic. A VUS should not be used for predictive testing of unaffected family members
Whole exome sequencing	Next generation sequencing to analyze all protein-coding regions (exons) in a genome
Whole genome sequencing	Analysis of an individual's entire DNA sequence including coding regions and non-coding regions
X-linked	Inheritance transmitted via the X chromosome

Supplemental Table 2. Common syndromes associated with congenital heart disease due to aneuploidy and microdeletions

Syndrome	Cardiac Anomalies	CHD %	Other Clinical Features
Trisomy 13	ASD, VSD, PDA, polyvalvular disease	80-100%	Microcephaly, holoprosencephaly, scalp defects, severe intellectual disability, polydactyly, cleft lip/palate, genitourinary abnormalities, omphalocele, microphthalmia
Trisomy 18	ASD, VSD, PDA, polyvalvular disease	80-100%	Prenatal growth deficiency, dysmorphic facies, clenched fingers, rocker-bottom feet, hypertonia, severe intellectual disability
Trisomy 21 (Down syndrome)	ASD, VSD, AVSD, TOF	40-50%	Dysmorphic facies, intellectual disability, conductive hearing loss
45, X (Turner syndrome /monosomy X)	CoA, BAV, dilation of ascending aorta, HLHS, PAPVD without ASD	20-50%	Short stature, shield chest with widely spaced nipples, webbed neck, lymphedema, primary amenorrhea
1p36 deletion	LV non-compaction cardiomyopathy, PDA	43-70%	Dysmorphic facies, intellectual disability, microcephaly, hearing loss, seizure disorder
5p15.2 deletion (Cri-du-chat syndrome)	ASD, VSD, PDA, TOF	10-55%	High-pitched cry, dysmorphic facies, intellectual disability, microcephaly, poor growth
7q11.23 deletion (Williams-Beuren syndrome)	Supravalvar AS, pulmonary artery stenoses	80-100%	Hypercalcemia, dysmorphic facies, intellectual disability, characteristic personality, renal disorders
22q11.2 deletion (DiGeorge or Velo-Cardio-Facial syndrome)	IAA Type B, aortic arch anomalies, truncus arteriosus, TOF	80-100%	Thymic and parathyroid aplasia/hypoplasia, dysmorphic facies, hypocalcemia, speech and learning disorders, psychiatric disease

CHD, congenital heart disease; ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus; HLHS, hypoplastic left heart syndrome; TOF, tetralogy of Fallot; PAPVD, partial anomalous venous drainage; CoA, coarctation of aorta; BAV, bicuspid aortic valve; AVSD, atrioventricular septal defect; IAA, interrupted aortic arch; AS, aortic stenosis

Supplemental Table 3. Common syndromes associated with congenital heart disease due to single gene defects

Syndrome	Cardiac Anomalies	Other Clinical Features	Causative Gene(s)
Alagille syndrome	PS, TOF, peripheral pulmonary stenosis	Bile duct paucity and cholestasis, typical facies, skeletal anomalies, ocular anomalies	*JAG1, NOTCH2*
Cardiofaciocutaneous syndrome	PS, ASD, HCM	Dysmorphic facies, ectodermal abnormalities, intellectual disability	*KRAS, BRAF, MAP2K1, MAP2K2*
Char syndrome	PDA	Dysmorphic facies and limb anomalies	*TFAP2b*
CHARGE syndrome	ASD, VSD, TOF	Coloboma, choanal atresia, intellectual disability, cranial nerve abnormalities, genital and/or urinary anomalies	*CHD7, SEMA3E*
Costello syndrome	PS, HCM, cardiac conduction abnormalities	Short stature, developmental delay, dysmorphic facies, increased risk of solid organ carcinoma	*HRAS*
Holt-Oram syndrome	ASD, VSD, AVSD, progressive conduction system disease	Pre-axial radial malformations (thumb abnormalities, radial dysplasia)	*TBX5*
Kabuki syndrome	ASD, VSD, TOF, CoA, PDA, TGA	Growth failure, intellectual disability, dysmorphic facies, spinal anomalies, cleft palate	*KMT2D, KDM6A*
Noonan syndrome	PS, ASD, HCM	Short stature, webbed neck, pectus deformity, dysmorphic facies	*PTPN11, KRAS, NRAS, HRAS, RAF1, SOS1, NF1, CBL, BRAF, SHOC2*

PS, pulmonic valve stenosis; AVSD, atrioventricular septal defect; HCM, hypertrophic cardiomyopathy; CoA, coarctation of aorta; TOF, tetralogy of Fallot; ASD, atrial septal defect; VSD, ventricular septal defect; TGA, transposition of the great arteries; PDA, patent ductus arteriosus

Supplemental Table 4. Genes associated with thoracic aortic aneurysms

Genetic Condition	Additional Clinical Features	Causative Gene(s) or genetic abnormality
Ehlers-Danlos Syndrome, vascular form	Thin, translucent skin, gastrointestinal rupture, rupture of the gravid uterus, rupture of medium to large-sized arteries	*COL3A1*
Familial thoracic aortic aneurysm and dissection	Thin translucent skin and arterial tortuousity (*TGFBR2*); PDA (*MYH11*); PDA, BAV, eye/skin abnormalities (*ACTA2*)	*TGFBR1, TGFBR2, MYH11, ACTA2*
Loeys-Dietz Syndrome (LDS) and others within LDS clinical spectrum	Bifid uvula or cleft palate, arterial tortuosity, aneurysms/dissections of other arteries, hypertelorism, skeletal features similar to MFS, craniosynostosis	*TGFBR1, TGFBR2, SMAD3, TGFB2, TGFB3, SKI*
Marfan Syndrome (MFS)	Mitral valve prolapse, tall stature, arachnodactyly, pectus abnormality, scoliosis, ectopia lentis, spontaneous pneumothorax, striae, dural ectasia	*FBN1*
Turner Syndrome	Bicuspid aortic valve, aortic coarctation, hypoplastic left heart syndrome, short stature, primary amenorrhea, webbed neck, low-set ears, low hairline, broad chest	45,X karyotype

PDA, patent ductus arteriosus; BAV, bicuspid aortic valve; MFS, Marfan syndrome.
Adapted from Circulation;2010;121:1544–1579.[21] ©2010 American Heart Association, Inc.

Supplemental Table 5. Types of genetic tests

Test	Format	Strengths	Limitations	Used for
Chromosome analysis	Examines chromosome structure	Detects trisomies, sex chromosome abnormalities, chromosomal translocations	Only detects major chromosomal abnormalities involving large DNA segments	Patients with multiple congenital anomalies
Fluorescent In-Situ Hybridization (FISH)	Fluorescent probes detect presence or absence of a specific chromosome region	Detects small chromosomal deletions not detectable by karyotype analysis	Only evaluates a specific genetic region	22q11.2 syndrome; 7q11.23 syndrome
Targeted deletion/duplication analysis	Multiple platforms including multiplex ligation dependent probe amplification and targeted array comparative genomic hybridization	Detects very small chromosomal deletions/duplications (involving only part of a gene) not detectable by FISH analysis	Only detects deletions/duplications involving genes included in the panel	Used when DNA sequencing doesn't identify a causative variant; can be used in place of FISH for specific syndromes
Chromosome microarray analysis	Oligonucleotides and/or SNPs tiled across the genome detect presence or absence of a specific chromosome region	Detects very small chromosomal deletions/duplications across the genome	Can identify small deletions/duplications of unknown significance	Patients with multiple congenital or developmental defects

Supplemental Table 5 (continued)

Sequencing (single gene/multiple gene panel)	DNA sequencing of specific gene(s)	Can detect single base pair genetic variants within coding sequence of a defined set of genes	Only tests a specific set of genes; test needs to be updated/repeated as additional causative genes are identified	Patients with identified or suspected cardiovascular conditions with defined genetic etiologies (e.g., HCM, ARVC, LQTS, CPVT, Marfan Syndrome, Loeys-Dietz Syndrome, Noonan Syndrome).
Sequencing (Whole exome) (WES)	Next generation sequencing of all coding DNA (1% of genome)	Can detect single base pair genetic variants within coding sequence of any gene	Identifies variants of uncertain significance. Insertions-deletions difficult to detect. Can lead to incidental findings that require further follow-up and evaluation	Patients in whom targeted genetic testing has not identified a causative variant
Sequencing (Whole genome) (WGS)	Next generation sequencing of all genomic DNA	Can detect single base pair genetic variants in coding and non-coding DNA	Identifies variants of uncertain significance. Can lead to incidental findings that require further follow-up and evaluation	Patients in whom targeted genetic testing (and possibly WES) has not identified a causative variant

HCM, Hypertrophic cardiomyopathy; ARVC, arrhythmogenic RV cardiomyopathy; LQTS, long QT syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia