Genetic testing is increasingly becoming possible for diagnosis, susceptibility testing, and prognostication in cardiovascular medicine. The practicing cardiologist, therefore, needs to be familiar with the clinical utilities and limitations of genetic testing. This review explores the major approaches to genetic testing and issues in test interpretation. Specific applications to cardiovascular diseases, including coronary artery disease, cardiomyopathies, cardiac arrhythmias, and pulmonary arterial hypertension are discussed. (J Am Coll Cardiol 2007;50:727–37) © 2007 by the American College of Cardiology Foundation

Advances in molecular genetics, and especially the sequencing of the human genome, are rapidly adding genetic tests to the armamentarium of diagnostic and predictive tools available for the management of cardiovascular disease. Genetic tests offer many advantages over traditional tests. They do not require invasive sampling, have high accuracy, and can be done at any time in life, whether or not symptoms of disease are present. Most physicians were trained before the advent of genetic testing and are unfamiliar with indications and intricacies of interpretation. Although the physician does not need to be intimately familiar with the details of genetic testing to appropriately order and interpret tests, some appreciation of the indications and limitations of genetic tests can help to insure that they are used to maximum benefit. In this review we will first provide background on the major approaches to genetic testing and the pitfalls in interpretation. We will then consider the role of genetic testing for the evaluation of patients with coronary artery disease (CAD), cardiomyopathies (CMs), cardiac arrhythmias, and pulmonary arterial hypertension (PAH). For each we will highlight the benefits and the limitations of testing and discuss what the future may bring.

General Principles of Genetic Testing

For purposes of this review, genetic testing is defined as the analysis of chromosomes, deoxyribonucleic acid, or ribonucleic acid to identify genetic variants that may be of medical significance. Most genetic tests involve direct detection of a mutation responsible for disease or risk of disease. Linkage-based tests rely on use of genetic markers that reside nearby a gene of interest to track inheritance of the gene in a family. This approach is used less often as the genes involved in disease risk are increasingly amenable to direct testing. A third approach, referred to as genomic testing, involves analysis of multiple genetic variants or products of gene expression to obtain an overall "genomic fingerprint" of an individual or tissue sample. This approach is in its infancy and will not be discussed further in this review.

Indications for genetic testing include 4 distinct applications: diagnostic testing, presymptomatic testing, predispositional (susceptibility) testing, and pharmacogenetic testing. Diagnostic testing is performed on an individual having signs and/or symptoms of disease with the goal of establishing a precise diagnosis. A genetic test can establish a diagnosis without the need to sample affected tissue and can serve as the basis for treatment, anticipatory guidance, and genetic counseling. Presymptomatic testing is applied to individuals who do not yet have signs or symptoms of disease, but are known to be at risk on the basis of family history. Genetic testing can determine risk of disease, but does not guarantee that disease will become symptomatic. Predispositional (susceptibility) testing applies to multifactorial disorders, where multiple genes interacting with one another and with the environment contribute to disease. Major research efforts are now being directed toward identification of genetic variants that can be used to predict risk of disease. Pharmacogenetic testing involves analysis of genes responsible for the metabolism and activity of drugs. Pharmacogenetic tests are likely to be used in the future to match the choice of drug to specific physiological targets, providing a greater likelihood of efficacy and fewer side effects.

The ability to offer a genetic test is not sufficient reason to include it in routine medical practice. Evaluation of a test includes consideration of analytical validity, clinical validity, and clinical utility. Analytical validity is defined as the...
likelihood that the reported results are correct (e.g., a specific genetic variant is present or absent). Genetic tests tend to have a high degree of analytical validity, barring human errors such as sample mix-up. Clinical validity is the degree to which the test correctly assesses the risk of health or disease. Genetic tests may reveal variants of unknown significance, and often do not identify all possible mutations; therefore, false-positive or false-negative results may occur. Clinical utility is the degree to which the test guides medical management. There are many instances where a test can be performed to indicate risk of disease, yet there is no approach to management that improves outcome based on the results of testing. Genetic testing must also be viewed in the context of ethical, legal, and social concerns, including risks of stigmatization, discrimination, anxiety, guilt, and so on.

**CAD and Myocardial Infarction (MI)**

Coronary artery disease is the leading cause of death in the world, affecting 13,000,000 people in the U.S. alone (1,2). As such, it is a major public health concern, and significant efforts have sought to reduce the mortality and morbidity associated with CAD. These efforts have focused primarily on modification of environmental and behavioral risk factors, including sedentary lifestyle, smoking, obesity, and high-fat diet. Modifying these behaviors is extremely important, and has been shown to reduce cardiovascular mortality and morbidity. Nonetheless, family history remains the single strongest independent risk factor for development of CAD (3). However, in most cases this risk cannot be determined more precisely. The information gained through a detailed family history does not identify specific interventions to limit risk, nor can it assist in determining a treatment plan. Thus, identification of specific genetic risk factors is essential for more precise risk determination, as well as individualization of therapy. Testing for such factors will be beneficial not only for those with a positive family history, but also could benefit healthy individuals with no family history. Although such uses of genetic tests are not currently available, the pace of discovery promises clinically useful tests in the near future.

**The difficulty of finding CAD-related genes.** The last few years have seen a remarkable series of advances in our understanding of the role of genetics in cardiac diseases. Disease-causing gene mutations have been identified in approximately two-thirds of cases of hypertrophic cardiomyopathy (HCM), nearly that much of dilated cardiomyopathy (DCM), and most instances of familial cardiac arrhythmias (4). Understanding the genetic basis of CAD, however, has proven more elusive. Except for rare forms that follow a Mendelian inheritance pattern, CAD is a multifactorial trait, caused by both genetic and environmental factors. Unlike single gene disorders, genetic studies of complex traits such as CAD are compounded by the lack of a perfect cosegregation between the risk allele and the phenotype and the high prevalence of the risk allele in the population. In a complex trait, the presence of a risk allele is neither necessary nor sufficient to cause the phenotype, and, hence, establishing causality is difficult. This is particularly the case for the results of allelic association studies performed with selective single nucleotide polymorphisms (SNPs) in small populations. The results of such studies are not sufficiently conclusive to confer clinical utility. The difficulty, while common to complex traits, also extends to CAD with a Mendelian inheritance pattern, as was recently demonstrated for the putative role of MEF2A in susceptibility to CAD.

MEF2A was identified through study of a large family with multiple members with early-onset CAD (5). It was assumed in this family that CAD was inherited as an autosomal dominant trait, and linkage analysis mapped the causative gene to a segment on chromosome 15q26, a region that contained 93 genes. In 1 of those genes, MEF2A, a 21-base pair deletion was identified in the members of this family that cosegregated with inheritance of CAD. MEF2A was also considered to be an attractive candidate gene because it is expressed in the developing vasculature of embryonic mice. In a follow-up study, 3 different genetic variations were identified among 207 individuals with CAD. The investigators suggested that MEF2A was a significant contributor to CAD, accounting for almost 3% of cases (5). A subsequent study called these findings into question (6), however. Not only did the investigators fail to identify variations in MEF2A among 300 patients with premature CAD, but they also found the same 21-base pair deletion in an elderly control subject. These findings cast doubt on the original association of MEF2A as an important gene in CAD, but more importantly highlight the difficulty in gene identification for complex traits like CAD (7).

Although the association of MEF2A and CAD remains unresolved, a number of other genes have been implicated in susceptibility to CAD (4). These can be divided into 2
groups: genes in which mutations directly cause CAD and those that convey a risk for (or protection from) CAD. Among the best-established genetic risk factors for CAD are single-gene disorders affecting plasma levels of low-density lipoprotein (LDL) cholesterol and high-density lipoprotein cholesterol. Genes responsible for familial hypercholesterolemia (FH) and Tangier disease are the prototypic examples of causal genes for CAD and MI. Familial hypercholesterolemia is an autosomal dominant disorder that is characterized by severe elevations in total serum cholesterol and LDL cholesterol. Cholesterol deposition accounts for the associated findings, which include tendon xanthomas and atheromas, and markedly elevates the risk for CAD and MI. The underlying defect is in the LDL receptor, which is responsible for the majority of uptake of circulating LDL by the liver. Familial hypercholesterolemia is an uncommon disorder, affecting 1 in 500 persons worldwide. Homozygosity for an associated FH mutation produces markedly elevated LDL and cholesterol levels, leading to progressive CAD and MI in the first decade of life. Familial hypercholesterolemia is genetically heterogeneous, and can be caused by mutations in a number of genes. These include the genes for the low-density lipoprotein receptor (LDLR), Apo-B-100, PCSK9, CYP7A1, and ARH.

Tangier disease is a rare autosomal recessive disorder that involves diffuse deposition of cholesterol esters throughout the reticuloendothelial system. The disorder is associated with the classic manifestation of enlarged yellow tonsils. It is characterized by low-to-absent plasma high-density lipoproteins and low cholesterol, due to mutations in ABCA1 gene.

The genes for these diseases were identified by linkage analysis, as each segregates in a Mendelian pattern with a clear marker for the presence of the mutant gene. For each disorder, clinical genetic testing is available. Efficacy of testing is limited to confirmation of the clinical diagnosis in a patient with an abnormal lipid profile, or for prenatal diagnosis. The real power of genetic testing is to identify at-risk individuals who cannot be otherwise identified, since they lack other clinical or laboratory markers.

Susceptibility genes for CAD. While mapping the causal gene for a monogenic disease is relatively simple, the process of mapping the susceptibility genes for a complex trait such as CAD is quite complex. The process is compounded by the lack of perfect cosegregation of a genetic marker with inheritance of CAD, genetic heterogeneity of CAD, low penetrance of the susceptibility allele, and high frequency of susceptibility alleles in the population. Accordingly, enthusiasm for the results of any single allelic association study for CAD must be tempered until it has been replicated and validated. In general, SNPs in genes regulating plasma levels of lipoproteins, inflammatory markers, and coagulation factors are the prime susceptibility alleles for CAD and MI. For example, apoE4 is among the most commonly established risk factors for CAD. Another example is the upstream transcription factor 1 gene (USF1), which has been linked to familial combined hyperlipidemia (8). Familial combined hyperlipidemia is characterized by elevated total serum cholesterol and triglycerides and is found in 20% of patients with CAD. Several genes involved in the inflammatory response may also be related to the development of CAD. Examples include SNPs in the genes encoding cytokine gene lymphotoxin-α (LTA), 5-lipoxygenase–activating protein (ALOX5AP), and phosphodiesterase 4D (PED4D) (9–11). However, the results have not been concordant in all studies (12). Recently, an SNP was identified that seems to confer a protective effect from CAD. The gene, LGALS2, is a regulator of other inflammatory genes, including LTA. This common polymorphism causes a 50% decrease in gene expression, and was found to be associated with a reduced risk for CAD (13). Although intriguing, this finding has yet to be confirmed.

Clinical applications. Genetic testing is expected to afford the opportunity for assessment of individual’s risk profile, not only in members of high-risk families but also in the general population, as part of routine health care. The expectation is that it will be possible to lower the risk for CAD, either by specific drug therapy, lifestyle modification, or a combination of both.

For individuals already affected by CAD, identifying the genetic basis might permit a particular therapy that targets the specific pathogenic mechanism underlying atherogenesis. Along these lines, research for 2 genes, ALOX5AP encoding arachidonate 5-lipoxygenase–activating protein, or FLAP, and leukotriene A4 hydrolase, now show promise for more specific therapies (14,15). A randomized placebo-controlled crossover study was conducted on the effects of a leukotriene inhibitor DG-031 in 191 patients with prior MI who had the at-risk genotypes for ALOX5AP and leukotriene A4 hydrolase. Patients in the treatment group showed reduction in circulating inflammatory biomarkers, suggesting a beneficial effect for this genetic subtype of CAD patients. This is among the first of what will be many trials that seek to translate genetic discovery to clinical utility (16).

Recommendations:
1. At present, there are no commercially available genetic tests for variants associated with CAD or MI that are recommended for routine care. Several academic medical centers are currently offering clinical trials for families or individuals at elevated risk for CAD or MI to help further elucidate useful gene or protein targets for risk stratification or pharmacogenetic approaches to care.
2. Testing is available for FH specifically targeting the LDLR gene by DNA-sequencing and Apo-B by mutation analysis. Genotypic-positive individuals should still be managed based on routine cholesterol assays and cholesterol guidelines; however, the likelihood for required multiple drug therapy is elevated. Patients and families affected by FH may benefit from genetic testing by providing early screening for the phenotypic appearance of elevated cholesterol levels and risk-factor modification before onset of disease (17).
CMs
The pace of genetic discovery for the various forms of CMs has proceeded rapidly, far greater than for CAD (Table 1). This is because, unlike the complex genetic inheritance for CAD, the genetically determined CMs tend to follow Mendelian inheritance patterns. Therefore, the strategies for identifying CM genes are more straightforward. In turn, genetic testing for variants associated with CM is far more advanced, with tests for several forms of CM already available clinically.

Cardiomyopathy is typically divided into several subtypes: dilated, hypertrophic, arrhythmogenic right ventricular dysplasia, restrictive, and unclassified (18).

DCM. Dilated cardiomyopathy is characterized by an increase in left ventricular end-diastolic diameter (>2.7 cm/m²) and reduced left ventricular systolic function (ejection fraction of <0.45). Dilated cardiomyopathy is among the most common causes of heart failure in the young and a major reason for cardiac transplantation. The overall prevalence of DCM in the U.S. is 36.5/100,000 (2). About 35% to 50%
of cases have a positive family history (19). In addition, about 10% of asymptomatic relatives of probands with DCM have evidence of unrecognized left ventricular dysfunction (20). Every inheritance pattern has been noted, including autosomal dominant and recessive, X-linked, and maternal (mitochondrial) forms, although the autosomal dominant forms are the most common.

Familial dilated cardiomyopathy (FDCM) can be further divided into 2 subtypes—isolated FDCM and FDCM with cardiac conduction defects. Both exhibit genetic heterogeneity, as over a dozen different chromosomal loci have been mapped to contain DCM-related genes (Table 1). Mutations in several genes have been associated with isolated (pure) DCM, including the genes encoding cardiac actin, desmin, α-tropomyosin, β-myosin heavy chain, cardiac myosin-binding protein C gene (21) (Table 1). Mutations in many of the genes that cause DCM also can cause HCM, as illustrated by mutations in β-myosin heavy chain and cardiac troponin T (22).

Dilated cardiomyopathy associated with cardiac conduction defects (DCM-CCD) is an autosomal dominant condition that typically presents in the second decade with mild cardiac conduction defects, which often progress to complete heart block. Unrecognized progression to complete heart block can cause sudden cardiac death. Atrial conduction defects and atrial fibrillation occur in a significant number of patients. Dilated cardiomyopathy develops independently of the conduction defect. Four loci have been mapped that contain DCM-CCD genes, but only 1, lamin A/C, has been identified (23). Mutations in lamin A/C also cause a variety of disorders, including Emery-Dreifuss muscular dystrophy and a mild skeletal myopathy associated with FDCM. Clinical testing for mutations in lamin A/C is available.

There are several forms of X-linked DCM. Duchenne and Becker muscular dystrophies are the prototypic representatives of X-linked DCM. The phenotype is due to progressive degeneration of muscle function and often starts as mild but progressive skeletal myopathy and DCM. Duchenne and Becker muscular dystrophies present in early childhood (Duchenne) or later in life (Becker), and for each, DCM is a later-onset manifestation (24). Cardiac involvement includes atrioventricular block, which is progressive; atrial arrhythmia and standstill; wall motion abnormalities; and DCM. Dilated cardiomyopathy may be the only cardiac manifestation of Duchenne/Becker muscular dystrophy. Dilated cardiomyopathy is present in approximately 90% of the advanced cases. Dilated cardiomyopathy presents with rapidly progressive disease in men in the second decade, ending in death or cardiac transplantation (25,26). Female carriers usually present in their 50s with a milder and more slowly progressive disease (26). The causal gene is dystrophin, which codes for a large cytoskeletal protein. The spectrum of mutations includes point, deletion, and insertion mutations or gene rearrangements. Frameshift mutations are associated with a severe form, while missense mutations or in-frame deletions or duplications often lead to a mild form of the disease.

The second form of X-linked DCM is seen as part of Barth syndrome. This disorder is characterized by neonatal heart failure, neutropenia, and myopathy (27). Urine organic acid analysis demonstrates elevations in 3-methylglutaconic acid, and mitochondrial abnormalities are seen by electron microscopy and functional studies (28). The type of cardiac defect is variable, including endocardial fibroelastosis, DCM, and noncompaction of the ventricular myocardium. Susceptibility to infection may prove fatal in the neonatal period, but most children survive and the DCM typically persists (27). The gene for Barth syndrome is G4.5, encoding tafazzin, a protein of unknown function (29). Different mutations in this gene can cause X-linked infantile DCM and endocardial fibroelastosis, as well as isolated noncompaction of the ventricular myocardium (INVM) (30,31).

Dilated cardiomyopathy is also part of the phenotypic expression of Emery-Dreifuss muscular dystrophy, which is an X-linked disorder characterized by progressive skeletal and cardiac myopathy. Cardiac involvement also includes arrhythmia, conduction defects, and sudden cardiac death. The responsible gene is EMD, which encodes emerin. Emerin is a member of the nuclear lamina-associated protein family.

Recommendations:

1. Genetic testing and mutation screening is not yet available for routine use, partly because of the extensive genetic heterogeneity of the disease. However, genetic diagnosis and mutation screening could be performed in families with several affected members through linkage analysis and screening of the candidate genes in the mapped locus.

2. The prevalence of causal genes and mutations has yet to be determined. Therefore, given the allelic and locus heterogeneity, routine genetic testing is not feasible in sporadic cases.

3. An electrocardiogram (ECG) and echocardiogram should be performed on family members of those with idiopathic DCM for screening. Up to 25% of family members may show abnormalities, including isolated left ventricular enlargement with or without systolic dysfunction. Patients with left ventricular enlargement and normal systolic function should be monitored routinely with echocardiography (32).

HCM. Hypertrophic cardiomyopathy is a primary disorder of cardiac myocytes, clinically recognized by the presence of cardiac hypertrophy in the absence of an increased external load. Pathologically, it is characterized primarily by the triad of myocyte hypertrophy, disarray, and interstitial fibrosis. Cardiac hypertrophy is asymmetric in approximately two-thirds of the cases, with the septum being the predominant site of involvement. Global systolic function is increased and diastolic function is impaired. In approximately 25% of the cases, there is significant left ventricular outflow tract
obstruction (19). Hypertrophic cardiomyopathy is a relatively common disorder: 1 study (33) found echocardiographic evidence of HCM in 1 of 500 young adult subjects. Hypertrophic cardiomyopathy most commonly presents in the 10- to 25-year age group, but presentation in infancy or in later adulthood is also seen.

Hypertrophic cardiomyopathy is a disease of the sarcomere, the basic unit of the heart muscle (34). The causal genes all encode sarcomere proteins: β-myosin heavy chain, cardiac regulatory and essential myosin light chains, myosin binding protein C, α-cardiac actin, α-tropomyosin, titin, and cardiac troponins T, I, and C (19). Mutations in the β-myosin heavy chain and myosin-binding protein C genes account for approximately 60% of familial and sporadic cases (35). Clinical testing for variants in most of these genes is available, and can provide valuable therapeutic and prognostic information (36).

Limited genotype-phenotype correlations were initially described from large multigenerational family studies. These findings included troponin T mutations, which are typically associated with a high risk of sudden cardiac death, despite the apparent mild or even subclinical hypertrophy. Mutations in myosin-binding protein C have been associated with a milder and later onset disease. Some mutations in the β-myosin heavy chain gene are associated with mild or even benign clinical course, while others cause a malignant form of HCM with presentation in early childhood, rapid progression of hypertrophy, and increased risk for sudden death (35). However, these findings have been observed consistently, and various clinical manifestations have been reported in patients with identical causal genes and mutations. Overall, there is considerable variability in the phenotypic expression of HCM, which is partly determined by the causal genes and mutations and partly by various modifying factors (37). The identity of these modifying factors is not fully known, but may include lifestyle, environment, genes, or epigenetic factors.

HCM phenocopy. Several other genetic disorders include cardiac hypertrophy as one component. Although cardiac hypertrophy in these conditions appears similar to HCM caused by sarcomeric mutations on echocardiographic examination, differences are apparent on tissue histology as well as pathogenesis. Therefore, the phenotype is referred to as HCM phenocopy and not true HCM. Examples of such disorders include glycogen storage diseases, respiratory chain enzyme defects, and Fabry disease. While cardiac hypertrophy is a serious complication for these disorders, the conditions typically present with other abnormalities. Fabry disease is worth noting, as studies have shown that up to 6% of affected men have HCM phenocopy (38), and 12% of carrier women may develop later-onset HCM phenocopy (39). Fabry CM may also present as a restrictive cardiomyopathy (RCM). Fabry disease is an X-linked disorder caused by accumulation of glycosphingolipid due to a defect in the enzyme α-galactosidase A. Predominant symptoms involve the skin, kidneys, and central nervous system; one subtype presents primarily with cardiac manifestations. Fabry disease is one of the few genetic disorders for which there is a specific treatment. Enzyme replacement therapy by regular infusions of agalsidase beta (Fabrazyme) has been shown to reduce symptoms and even reverse disease progression (40). Such therapy must be maintained for life, or disease progression will resume.

Recommendations:

1. Mutation analysis for the 8 sarcomeric genes is now commercially available for clinical testing (however, the cost may be prohibitive, total cost >$4,000), as many insurance companies do not cover the test. Furthermore, due to the heterogeneity of the HCM, a negative test does not exclude the possibility that an individual's HCM is due to a mutation in a gene that was not tested.

2. Maron et al. (33) have proposed a screening mechanism for high-risk individuals (e.g., those with family history of HCM) who are unable to utilize genetic testing, either because of cost/insurance issues or because the mutation could not be identified in an affected family member. In such families, adolescents between the ages of 12 to 21 years should have ECG and echocardiography screening on a 12–to 18-monthly basis. Patients under the age of 12 years require screening only if high-risk features such as malignant family history of premature HCM death/complication, they are a competitive athlete, or symptoms or clinical suspicion of early left ventricular hypertrophy exist. Patients older than 21 should continue ECG and echocardiography examinations every 5 years to exclude a late-onset HCM presentation.

3. Based on a readily available therapy and simplicity of the testing, patients with unexplained concentric left ventricular hypertrophy should be screened for Fabry disease with a plasma alpha-galactosidase A level.

Arrhythmogenic right ventricular dysplasia cardiomyopathy (ARVC). Arrhythmogenic right ventricular dysplasia/cardio myopathy is characterized by fibrofatty replacement of myocytes predominantly in the right ventricle, and sometimes in the left ventricle. This replacement may be localized, and can result in the formation of ventricular aneurysms in affected areas (41). Cardiac failure, initially right heart failure and in advanced cases left heart failure, may result. In the latter situation, the clinical presentation may mimic DCM. Sudden cardiac death due to an arrhythmia is a more common cause of death, especially in younger individuals. Although the exact prevalence of this disorder is not known, ARVC may be the second most common cause of sudden unexpected cardiac death in otherwise healthy young adults (34).

A history of affected family members is found in 30% to 50% of patients (42) and follows an autosomal dominant inheritance pattern. An autosomal recessive form in conjunction with skin and hair disorders also has been described and referred to as cardiocutaneous syndrome. To date, 8 chro-
mosomal loci have been mapped (43), and 4 genes encoding desmosomal proteins have been identified: plakoglobin (44), desmoplakin (45), desmoglein 2, and plakophilin 2 (46). Recently, mutations in plakophilin 2 were shown to be the most common cause, found in over one-half of cases in one study (42). Mutations in ryanodine receptor 2 cause catecholaminergic polymorphic ventricular tachycardia (CPVT), which could mimic ARVC (phenocopy) (47). Mutations in the regulatory regions of transforming growth factor β3 have been associated with ARVC (48), but causality has not been established.

Recommendations:
1. Current data raise the possibility of routine genetic testing for variants associated with ARVC. Screening of the 4 known genes encoding desmosomal proteins could lead to identification of the causal mutation in about two-thirds of the cases. However, there is no commercially available genetic test for diagnosis of ARVC.

RCM. Restrictive cardiomyopathy is a primary myocardial disease, characterized by impaired ventricular diastolic filling, normal or small ventricles, enlarged atria, and often preserved global systolic function. The clinical phenotype of RCM also occurs in various conditions such as amyloidosis, sarcoidosis, and Fabry disease.

Familial RCM exhibits an autosomal dominant form of inheritance. It could occur in conjunction with skeletal myopathy and atrioventricular conduction defects. Two causal genes, namely DES and TNNI3, which encode desmin and cardiac troponin I, have been identified. Desmin is an intermediary filament that is also involved in desmoinopathies, involving skeletal muscles as well as the heart. Mutations in TNNI3, which are known to cause HCM and DCM, also cause RCM. Restrictive cardiomyopathy also occurs in patients with Noonan syndrome, a disease caused by mutations in protein tyrosine phosphatase, nonreceptor type II. The utility of genetic testing in RCM remains to be established.

Unclassified CMs. Isolated noncompaction of the ventricular myocardium is a poorly understood, rare, but probably underdiagnosed disorder. It is often diagnosed phenotypically as DCM or HCM. The characteristic manifestations include prominent trabeculation and deep recesses within the endocardium in the absence of coexisting structural heart anomalies (49,50). Isolated noncompaction of the ventricular myocardium is diagnosed based on echocardiographic findings of segmental thickening of the left ventricular myocardial wall with a ratio of noncompacted to compacted myocardium of <2:1 at end-systole. It is genetically distinct from the NVM associated with Barth syndrome (51). Isolated noncompaction of the ventricular myocardium is thought to be a developmental anomaly, an arrest of in utero cardiac muscle development.

The clinical presentation for INVM is variable. Early reports suggest a poor prognosis, with a high rate of progression to heart failure and death or transplantation. However, subsequent reports have shown that INVM is, in fact, associated with a variable clinical course (50,52,53).

Isolated noncompaction of the ventricular myocardium is genetically heterogeneous. To date, 4 different genes and 1 genetic locus have been associated with INVM. In addition to G4.5, these include alpha-dystrobrevin (DNTA) (54), Cypher/ZASP (55), and lamin A/C (LMNA) (56). Only a small percentage of cases to date have been found to have mutations in any of these 4 genes, with most being associated with G4.5/TAZ (31,51). Recent linkage analysis of a family with INVM has identified an additional locus on 11p15 that is associated with autosomal dominant INVM in 1 family (57). The range of clinical variability is, as yet, not known (58).

Recommendations:
1. While several genes are known, there is insufficient data to advocate genetic testing for diagnosis and prognostication in INVM.
2. Family screening by genetic studies is at present not recommended. Echocardiographic screening of family members of affected individuals is recommended (59).

Familial cardiac arrhythmias. Like CM, many genes involved in familial arrhythmias have been identified in the last 15 years. Genetic studies have illustrated the genetic heterogeneity of the phenotypes, clinically recognized as a single entity. In addition, genetic studies suggest that each genetic form should be considered to represent a distinct entity (60).

Long QT syndrome (LQTS) is characterized by prolonged ventricular repolarization and a predisposition to polymorphic ventricular tachycardia (torsades de pointes). Three main subtypes exist: Romano-Ward syndrome, which is isolated LQTS inherited in an autosomal dominant manner; Jervell and Lange-Nielsen syndrome (JLNS), which is associated with sensorineural hearing impairment and is inherited as an autosomal recessive trait; and Andersen-Tawil syndrome, in which LQTS is one component of a more complex phenotype (61,62).

Genetic studies have demonstrated at least 10 different forms of LQTS, and several genes are involved in different clinical subtypes of LQTS, as well as other genetically determined arrhythmias (Table 2). KCNQ1 (LQT1) and KCNE1 (LQT5) encode for the alpha and beta subunits of the catecholamine-sensitive components of the potassium channel of the cardiac delayed rectifier. Mutations in these genes cause disease by a variety of mechanisms, including haploinsufficiency and dominant negative effect (63). Mutations in KCNQ1 are the most common in Romano-Ward syndrome, found in about one-half of affected individuals. Homozygous mutations in either KCNQ1 or KCNE1 cause the autosomal recessive JLNS.

KCNH2 (LQT2) and KCNE2 (LQT6) encode for the alpha and beta subunits of the rapid component of the potassium channel. Mutations in KCNH2 are the next most common cause of LQTS, accounting for 35% to 40% of
In contrast, KCNE2 is the least commonly identified mutation in LQTS. SCN5A (LQTS3) encodes the cardiac sodium channel. Mutations in this gene account for 10% to 15% of LQTS (63).

Until recently it was assumed that all LQTS-associated genes involved ion channels. The discovery that ANK2, the gene for the structural protein ankyrin B, LQTS4, demonstrated that other types of genes can cause LQTS (64). While only found in a single family to date, the ANK2 mutation seems to have a distinct clinical presentation, as most patients also manifest sinus bradycardia and paroxysmal atrial fibrillation. Although the mechanism of disease is uncertain, it may be that ankyrin B is involved in anchoring ion channels in the cell membrane.

Recently, several genotype-phenotype studies have shown that each LTQS subtype has its own clinical characteristics, including subtle differences in the ST-T complex, and different triggers and risks for cardiac events. For example, the risk for a cardiac event seems to be less for LQT1 compared with both LQT2 and LQT3 (65). Furthermore, each subtype has a significant rate of nonpenetration: LQT1 36%; LQT2 19%; and LQT3 10%. Lastly, mutations in the pore region of the LQTS2 gene KCNE2 carry a greater likelihood of cardiac disease than even nonpore mutations (66).

Such studies are very valuable in differentiating the risks for individual patients, and illustrate one manner in which clinical testing has an important role in the evaluation, management, and prognosis counseling for these patients (67). For example, an implantable cardioverter defibrillator is often used, but may be best for symptomatic individuals with the LQT3 phenotype (68) and one subtype of Romano-Ward syndrome, namely those patients who also manifest syndactyly (69). Lastly, genetic testing is obviously important in presymptomatic diagnosis of at-risk family members in order to prevent syncope and sudden death. Caution should be taken to ensure all first-degree relatives are tested, as individuals may have a normal QTc duration on ECG and yet be genotype positive with risk for sudden death (70).

Andersen-Tawil Syndrome is a rare autosomal dominant condition in which LQTS is associated with other manifestations, including a characteristic dysmorphic facial appearance (low-set ears, wide set eyes, small mandible, fifth digit clinodactyly, syndactyly, short stature, and scoliosis), and periodic muscle weakness (61,62). While the risk for adverse cardiac events is present, the condition is most often associated with a benign outcome (71). The responsible genetic change is in KCNJ2, which encodes the inward rectifier potassium channel 2.

**Recommendations:**

1. Individuals with the clinical diagnosis of LQTS are recommended to consider genetic testing after counseling, as there is evidence that genotype may help with direct optimal treatment strategies. Testing is currently available commercially. Not all insurance companies cover the costs of testing.

2. Genetic testing should be offered to all first-degree relatives regardless of QTc interval.

3. If the patient is determined to be genotype positive, consideration should be given to enrolling the patient in the International Long QT Registry.

**Other familial arrhythmias.** Catecholaminergic polymorphic ventricular tachycardia is a poorly understood condition in which individuals manifest a variety of ventricular and supraventricular arrhythmias during exercise or stress (72). Unlike LQTS, these occur in a predictable manner. In about one-third of cases, a family history will reveal an episode of sudden death in an otherwise well person, often in childhood.

Catecholaminergic polymorphic ventricular tachycardia is inherited as an autosomal dominant trait, with about 50% of patients having a mutation in RYR2, the gene for the

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<td>LQT5/KCNJ1*</td>
<td>2%–3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LQT6/KCNJ2*</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LQT8/CACNA1c</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LQT9/CAT3/SCN5A†</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LQT10/SCN4B</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Andersen-Tawil</td>
<td>AD</td>
<td>Physical dysmorphia; periodic paralysis</td>
<td>LQT7/KCNJ2*</td>
<td>~60%</td>
</tr>
<tr>
<td>Jervell and Lange-Nielsen</td>
<td>AR</td>
<td>Sensorineural hearing impairment</td>
<td>LQT1/KCNQ1*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LQT5/KCNJ1*</td>
<td></td>
</tr>
</tbody>
</table>

*Clinical testing is available; †mutations in SCN5A also cause Brugada syndrome and progressive cardiac conduction defects.

Abbreviations as in Table 1.
ryanodine receptor (73). A second gene, CASQ2, causes an autosomal recessive form of CPVT (74).

**Recommendations:**

1. Genetic testing for mutations associated with CPVT is commercially available and recommended based on the treatment option for presymptomatic individuals.

Brugada syndrome is a rare autosomal dominant condition characterized by the following electrocardiographic abnormalities in a structurally normal heart: elevated ST-segment in leads V1 to V3, incomplete right bundle branch block, and susceptibility to ventricular arrhythmias, which occur most often in sleep or at rest (75,76). It is caused by mutations in SCN5A, which is also the gene for LQT3. Unlike mutations in LQT3, which are gain of function, the mutations associated with Brugada syndrome are loss of function. SCN5A mutations also cause progressive cardiac conduction defect (PCCD or Lenegre disease). Progressive cardiac conduction defect is a common, but poorly defined, autosomal dominant condition that can lead to complete atrioventricular block, syncope, and sudden death (77).

Other mutations in SCN5A have been reported in families with manifestations suggestive of PCCD, Brugada syndrome, and LQT3 (78–80). While there is limited correlation of mutations in SCN5A or other genes with the clinical presentation, the genetic mutation is clearly not the sole explanation for the observed phenotype (60). Understanding the interactions between these and other proteins is still incomplete, but will be needed if clinical testing is to provide the most useful information to patients, at-risk family members, and for population screening as well.

**Recommendations:**

1. Commercial testing is available for patients with suspected Brugada syndrome; however, the SCN5A gene accounts for only 25% to 30% of clinically affected patients. Although the yield is low, this testing may be helpful in borderline cases and for presymptomatic screening in related family members.

**Familial PAH.** Pulmonary arterial hypertension is an etiologically heterogeneous disease in which there is a progressive increase in pulmonary artery pressure, eventually leading to heart failure and death (81). The 2 types of PAH, the idiopathic and the familial form, although rare, constitute a significant portion of patients seen with this disease.

The genetic factors predisposing to primary pulmonary hypertension (PPH) are slowly being unraveled. A known family history of PPH occurs in 6% to 12% of all reported cases. This disease appears to be transmitted in an autosomal dominant pattern with incomplete penetrance and evidence of genetic anticipation (decreasing age at death in subsequent generations). Vertical transmission is readily apparent in most pedigrees, with many cases of father-to-son transmission, thereby excluding X-linkage. Linkage studies have mapped the disease locus to a 3 cM interval on chromosome 2q31-32 (locus PPH1) (82,83). Examination of candidate genes within this interval led to the identification of mutations in the BMPR2 gene, which predict a disrupted protein and tracks with the disease. Inactivating heterozygous mutations have been found throughout the BMPR2 gene in approximately 60% of patients with a family history and 26% of sporadic cases of PPH (84). The 1038-amino-acid BMPR2 protein comprises ligand-binding, kinase, and cytoplasmic domains. Mutations are now known to exist in each of the 13 exons that code for these specific regions. Interestingly, BMPR2 mutations have been identified in affected individuals with other risk factors for PPH, including fenfluramine (“Fen–Fen”) exposure (85).

**Recommendations:**

1. Due to the heterogeneity of mutations in PAH, broad use of testing for BMPR2 mutations is not recommended. However, testing among large families that may yield a significant number of asymptomatic carriers confers benefit and allows for early detection of phenotypic expression using screening mechanisms such as Doppler echocardiography or right heart catheterization with exercise.

2. In large affected families undergoing screening, the yield in testing for the currently known BMPR2 mutations remains less than 50%. Haplotype testing may be useful in these large families if enough affected and unaffected members exist (86).

**Conclusions**

The era of genomic medicine is just beginning, and already there are several new approaches to testing that enhance diagnosis and management of cardiovascular disease. New genetic tests for rare single gene disorders and more common multifactorial disorders will appear gradually but steadily over the coming years. This will change the approach to diagnosis, and will be a component of new approaches to preventative medicine. The physician will increasingly be called upon to be a sophisticated consumer of information that results from genetic testing. Ultimately, the major gift of genetics to medicine will not be in the identification of genes responsible for disease, but in elucidation of the molecular pathways that underlie health and disease. Genomic medicine will have come of age at a point when diagnostic, predictive, and predispositional tests are coupled to new approaches to prevention and management, informed by understanding of pathophysiology and armed with new targeted therapies.

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**REFERENCES**