Recent advances in the field of genetics have significantly enhanced our understanding of many cardiovascular conditions and improved diagnosis as well as management of these disorders. However, mendelian cardiovascular diseases still pose unique challenges to clinicians, especially when presented with inherited conditions that have a wide range of phenotypic presentations. In cardiovascular single-gene disorders with potentially devastating initial manifestations, such as sudden cardiac death (SCD) or aortic dissection, appropriate and prompt identification of individuals at risk is imperative. In addition, the management of the disease is not only applicable to the individuals at risk but also extends to other members in the family. Therefore, the general approach to patients with such diseases and their affected family members needs to be considered in the context of fundamental principles of mendelian inheritance. Numerous examples of cardiovascular mendelian disorders exist in which the importance of genetics has been clearly recognized, and most common monogenic cardiovascular disorders are transmitted in families in an autosomal dominant fashion. In such autosomal dominant disorders, it is important to remember the overriding principle that any first-degree relative of an individual with an autosomal dominant multigenerational familial cardiovascular disorder has a 50% chance of also being affected by this genetic trait. Thus, when added to a family history, any symptom or sign on history, clinical evaluation, or testing that is consistent with the diagnosis in question creates a >50% likelihood that the family member is affected by the disorder as well. In this review, we will focus on a few examples of such autosomal dominant disorders to highlight the current state of clinical practice in these mendelian disorders as shaped by classic and modern genetics.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is an important inherited cardiovascular disorder for which genetic principles have significant impact on our evaluation and approach to patients. HCM has an estimated prevalence of 1 in 500 in the United States and remains one of the most common causes of SCD in young people.1 HCM is characterized by left ventricular hypertrophy (LVH) with myocardial disarray and increased fibrosis triggering various symptoms due to diastolic dys-

function, left ventricular outflow tract obstruction, and potentially lethal arrhythmia. HCM is typically inherited in an autosomal dominant pattern, with most mutations occurring in genes that encode myocardial contractile proteins. Numerous mutations have been identified in >20 different genes to date (Table 1).2–11 Despite the high prevalence of this disorder, the annual mortality from HCM remains relatively low, and it still remains a challenging task for practicing clinicians to identify which individuals are at significant risk for SCD.12 Although the American College of Cardiology/American Heart Association guideline classifies implantable cardioverter-defibrillator (ICD) therapy as a class I indication in patients with sustained ventricular tachycardia (VT) or ventricular fibrillation, the real challenge is to identify these individuals before the onset of potentially catastrophic events.13

Relatively simple diagnostic modalities, such as echocardiography, can detect asymmetrical, marked LVH and assist in establishing a diagnosis of HCM. In addition, cardiac magnetic resonance imaging and computed tomography may detect additional characteristics suggestive of HCM.14–16 Despite the availability of these diagnostic tools, several features of HCM still pose diagnostic dilemmas for practicing cardiologists. Other conditions, such as athlete’s heart, coexisting hypertension, and aortic stenosis, can mimic HCM with similar hypertrophic morphologies. Distinguishing HCM from athlete’s heart is particularly important because an erroneous diagnosis can limit or even preclude talented athletes from participating in competitive sports.17 In addition, misdiagnosing HCM may result in SCD because HCM is the leading cause of cardiovascular death in young competitive athletes.18 Although a few diagnostic tools can aid in distinguishing athlete’s heart from HCM, it remains a difficult task for clinicians because of the genetic and phenotypic heterogeneity of the disorder.18,19 Deconditioning of athletes with ensuing reduction of wall thickness may aid in diagnosing athlete’s heart, but such a maneuver requires interrupting activity and training of competitive athletes for a prolonged period of time. Moreover, the age of onset of HCM varies from early childhood to late adulthood, which creates even further challenges for clinicians. Although identifying a mutation in 1 of the genes associated with HCM by genetic
testing may aid in confirming a diagnosis, a negative test result does not exclude a diagnosis of HCM in these athletes given the relatively low sensitivity of current genetic testing. As new clinical and genetic diagnostic modalities are being developed, there should be an eventual resolution of the controversy surrounding screening athletes for HCM.\

However, the importance of family history is undeniable, and it plays a major role when a diagnosis of HCM is made. In the presence of a strong family history of HCM, any sign of LVH (whether by imaging or by ECG) should be taken with caution, and HCM should be presumed unless an alternate diagnosis is confirmed without reservation (Figure). Although individuals who share the same gene defect, even in the same family, may have markedly different disease manifestations including extent of hypertrophy, hemodynamic impairment, and incidence of life-threatening arrhythmias, family members tend to have a greater likelihood of sharing disease manifestations than unrelated individuals with the same condition. Thus, prophylactic ICD should be considered when there is a strong family history of SCD. Furthermore, if an individual has a strong family history, a more meticulous screening for HCM is necessary even when LVH is not detected by initial screening ECG and echocardiogram. Because of variable penetrance and expressivity, even mild LVH that may not meet the arbitrary diagnostic criterion of 15 mm in septal thickness may represent HCM in the presence of strong family history.\n
Phenotypic manifestations may develop at a later age, and a full consideration of the diagnosis is necessary in young individuals without early signs or symptoms because the initial HCM manifestation may be catastrophic. The risk of sudden death associated with late-onset disease remains controversial. Current guidelines suggest that when an individual has been diagnosed with HCM, first-degree relatives <12 years of age should be screened by at least history, physical examination, ECG, and echocardiography every 5 years. First-degree relatives aged 12 to 22 years should be screened every 12 to 24 months, and for those aged ≥23 years, individuals should have repeated screening every 5 years or until genetic testing confirms the presence or absence of the disease-causing mutation in the family.\n
### Table 1. Genes Often Associated With HCM

<table>
<thead>
<tr>
<th>Genes</th>
<th>Proteins</th>
</tr>
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<tbody>
<tr>
<td>MYH7</td>
<td>β-Myosin heavy chain</td>
</tr>
<tr>
<td>MYH6</td>
<td>α-Myosin heavy chain</td>
</tr>
<tr>
<td>MYBP1C3</td>
<td>Cardiac myosin binding protein C</td>
</tr>
<tr>
<td>TNNT2</td>
<td>Cardiac troponin T</td>
</tr>
<tr>
<td>TNNT3</td>
<td>Cardiac troponin I</td>
</tr>
<tr>
<td>TNNC1</td>
<td>Cardiac troponin C</td>
</tr>
<tr>
<td>TPM1</td>
<td>α-Tropomyosin</td>
</tr>
<tr>
<td>MYL3</td>
<td>Myosin essential light chain</td>
</tr>
<tr>
<td>MYL2</td>
<td>Myosin regulatory light chain</td>
</tr>
<tr>
<td>ACTN2</td>
<td>α-Cardiac actin</td>
</tr>
<tr>
<td>TTN</td>
<td>Titin</td>
</tr>
<tr>
<td>TBOD3</td>
<td>LIM binding domain 3</td>
</tr>
<tr>
<td>CSRP3</td>
<td>Muscle LIM protein</td>
</tr>
<tr>
<td>TCAP</td>
<td>Telethonin</td>
</tr>
<tr>
<td>TCL</td>
<td>Vinculin/metavinculin</td>
</tr>
<tr>
<td>ACTN2</td>
<td>α-Actinin 2</td>
</tr>
<tr>
<td>MYOZ2</td>
<td>Myozin 2</td>
</tr>
<tr>
<td>JPH2</td>
<td>Junctophillin-2</td>
</tr>
<tr>
<td>PLN</td>
<td>Phospholamban</td>
</tr>
</tbody>
</table>

**Modification of Clinical Criteria by Family History in HCM**

- In the presence of family history, HCM needs to be considered and patients screened with serial echocardiography in the absence or presence of mild LVH (wall thickness of <15 mm) on initial evaluation.

Along with improvements in traditional diagnostic tools, recent advances in the genetics of HCM have considerably improved our understanding of HCM and influenced the clinical care of these patients. These advances now permit routine clinical deployment of genetic testing, which, in its current standard form, screens the 8 most common causative genes for mutations. Unfortunately, despite potential commercial laboratory claims to the contrary, currently available genetic testing has a sensitivity of <70% and is not a practical initial screening tool in asymptomatic patients. Nevertheless, the identification of a gene mutation provides a definitive diagnosis of HCM in affected individuals and identifies family members at risk for developing overt HCM. Furthermore, affected patients with SCD can undergo genetic screening for these mutations to identify and appropriately manage family members at risk.

As more HCM-causing mutations have been discovered in various genes, several attempts have been made to associate
specific genes/mutations with HCM severity and outcomes to define further a role of genetic testing in the management of individual HCM. One early study proposed that a mutation involving troponin T is strongly associated with SCD, and other studies revealed a relatively benign phenotype for mutations involving myosin binding protein C. Numerous similar observations were made in regard to mutations in other genes as well. However, these studies were performed with relatively small cohorts, and other studies in unrelated cohorts have not always produced similar findings. In a more recent longitudinal study of a large unrelated cohort, it was shown that patients with mutations in genes encoding myofilament proteins have more severe phenotypes, including left ventricular dysfunction and increased risk of combined end points of death, stroke, and heart failure. However, prognostication in HCM patients based on molecular genetics remains elusive, and it awaits both further advances in understanding genetic modifiers in this single-gene disorder as well as refinement of genotype-driven therapeutic strategies.

Nonetheless, it cannot be overemphasized that even if molecular genetic testing does not routinely provide risk stratification in HCM, assessment of family history still provides an important adjunctive tool in clinical decision making. To prevent SCD, American College of Cardiology/American Heart Association guidelines recommend primary prevention with ICD implantation in those patients with 1 or more major risk factors. Major risk factors include not only a personal history of cardiac arrest, VT, unexplained syncope, left ventricular thickness ≥30 mm, and abnormal exercise blood pressure but also family history of premature sudden death (Table 2). Individuals with HCM associated with SCD should be presumed to carry a “malignant” mutation, and care should be taken with the immediate family members. Regardless of the actual genotype, these probands should be carefully screened for any findings suggestive of HCM, and ICD implantation for primary prevention should be considered once they are diagnosed. As noted above, a lack of current clinical findings should be followed by periodic reevaluation in patients with strong family history because such patients may yet manifest HCM features in the future.

Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is another mendelian cardiomyopathy that is a well-recognized cause of SCD. With a prevalence of 1 in 5000 and a predilection for men in the second to fourth decades of life, ARVC is an autosomal dominant disorder characterized by fibrofatty replacement of the right (and less commonly left) ventricle with a wide range of clinical presentations ranging from palpitation, syncope, and heart failure to SCD. An international task force has recommended criteria to diagnose ARVC in an individual. These include major and minor criteria based on characteristic structural abnormalities, tissue characterization, ECG changes, arrhythmia, and, in recognition of the inherited basis of the disorder, family history. Modern advances in diagnostic imaging such as cardiac magnetic resonance imaging have significantly improved diagnostic accuracy and have been particularly helpful in differentiating ARVC from other more benign disorders, such as right ventricular outflow tract VT. However, diagnosing ARVC remains challenging at times for many clinicians; a significant portion of ARVC patients may be missed even with current diagnostic criteria because of variable expressivity of the mutant genotype over the course of the disorder.

Furthermore, SCD is frequently the initial presentation of ARVC. Thus, it is imperative to identify patients at risk early, before clinical presentations that would make patients eligible to meet task force criteria.

Several genes have been implicated in the pathogenesis of ARVC. The prevalence of mutations in various desmosomal genes has been studied in several studies of unrelated ARVC cohorts (reviewed in Reference 50). Pooled results of these studies indicate that the desmosomal genes currently known to cause ARVC account for disease in <50% of ARVC patients, and therefore these findings have limited value in clinical practice. Certainly, identification of a mutation in the aforementioned genes in an individual with ARVC is valuable for allowing genetic screening of family members of the proband. Detection of such mutations may identify individuals at risk, which is especially important in the setting of a strong family history of SCD. These individuals can be subjected to more stringent screening for potential signs of ARVC and to allow preventative ICD therapy. Furthermore, they can be counseled about the 50% chance of passing these mutations to their offspring. Family members without inherited mutations can be reassured and can avoid undergoing serial evaluations over the course of their lives, and emotional trauma from the chronic fear of potential catastrophic events can be prevented.

However, as in the case of HCM, ARVC genetic testing currently has inadequate sensitivity to exclude the diagnosis in individuals who are asymptomatic or who do not meet task force criteria. Thus, it is essential for clinicians to subjectively weigh a family history of ARVC, particularly in patients who are first-degree relatives of affected individuals, because a diagnosis is considered and risk stratification is performed in cases in which marginal clinical evidence is available to support the diagnosis. As with other autosomal dominant disorders, first-degree relatives of individuals with known familial ARVC have a minimum 50% a priori likelihood of being affected by ARVC before physical findings and imaging data are considered. The most recent practice guideline from the Heart Failure Society of America recom-
organ systems. Some characteristic skeletal manifestations include T-wave inversion in right precordial ECG leads, VT with left bundle branch pattern, and mild dilatation and hypokinesia of the right ventricle.

**Modification of Clinical Criteria by Family History in ARVC**
- If family history of ARVC has been confirmed at surgery or autopsy, 1 additional major criterion or 2 minor criteria are needed to make the diagnosis.
- In the presence of family history of ARVC (clinical diagnosis) or SCD (age <35 years) suspected as a result of right ventricular dysplasia, 1 major criterion plus 1 additional minor criterion or 3 additional minor criteria are needed to make the diagnosis.

**Marfan Syndrome**
Marfan syndrome is another example of mendelian cardiovascular disease in which the impact of genetics and family history has become increasingly significant. Marfan syndrome occurs in 1 in 3000 to 5000 individuals. It is an autosomal dominant condition caused by fibrillin-1 gene (Fbn-1) mutations encoding for the extracellular matrix protein fibrillin, an integral component of connective tissue.

Fibrillin-1 plays a significant role in transforming growth factor-β signaling, and transforming growth factor-β receptor mutations have been identified in some patients with phenotypes similar to Marfan syndrome but without fibrillin-1 gene mutations. Marfan syndrome is a systemic connective tissue disorder characterized by manifestations involving multiple organ systems. Some characteristic skeletal manifestations of this syndrome include disproportional increase of linear bone growth resulting in malformations of the digits (arachnodactyly), pectus excavatum/carincatum, increased arm and leg length, scoliosis, and craniofacial abnormalities. Common ocular involvement is lens dislocation in 1 or both eyes (ectopia lentis) and severe myopia. Cardiovascular manifestations include progressive aortic root enlargement and ascending aortic aneurysms, possibly leading to aortic regurgitation, dissection, or rupture, as well as mitral valve prolapse.

Among these various organ involvements, aortic dissection and rupture remain the leading causes of deaths in patients with Marfan syndrome. Therefore, a critical part of managing Marfan patients is screening and following aortic root dilatation in order to perform elective aortic root replacement before a potentially catastrophic event. Absolute size of the proximal aorta has been shown to predict risk of aortic dissection or rupture, and prophylactic surgery is recommended if the aortic size exceeds 5 cm at the level of the sinus of Valsalva. However, the phenotype may vary depending on age and especially family history in Marfan syndrome. An aortic diameter <5 cm may still confer an increased risk of dissection and/or rupture in individuals with family history of aortic dissection at a relatively young age or with relatively rapid aortic enlargement (≥5 mm in a year). Identification of aortic enlargement and grading of its severity are best done by relating aortic diameter to that expected for a given individual’s age and body size. Following aortic size in relation to established nomograms or quantified as Z scores allows more precise monitoring of aortic size as well as rate of growth to intervene before catastrophic events, such as aortic dissection or rupture.

Although Marfan syndrome has been described and studied for many decades, accurate diagnosis of the disorder remains a clinical challenge. Other connective tissue disorders frequently have partially similar phenotypes overlapping with Marfan syndrome, and current diagnostic criteria now clearly classify conditions previously identified as Marfan syndrome as distinct disorders (eg, the Loeys-Dietz syndrome). Furthermore, the variable age of onset of different phenotypes provides further difficulty in identifying individuals with the syndrome. Diagnostic criteria have been refined recently to improve accurate identification of Marfan patients. Moreover, the identification of fibrillin-1 gene mutations has fostered new opportunities for the diagnosis of Marfan syndrome. However, genetic testing for fibrillin-1 mutations is insufficient by itself for the diagnosis. Although the sensitivity of fibrillin-1 mutations is >90%, these mutations display poor specificity because of other connective tissue diseases that share mutations in these genes, such as familial ectopia lentis. As the genetic bases of Marfan syndrome and other connective tissue disorders have become more clear, the need for more systematic and stringent criteria has become apparent. The “Ghent” criteria, currently the most widely used diagnostic criteria, were originally developed on the basis of major and minor clinical manifestations of cardiovascular, pulmonary, skin/integument, skeletal, and ocular systems along with the family history and genetics.

However, some of the more nonspecific criteria included in the Ghent nosology have caused confusion with non-Marfan connective tissue disorders with overlapping phenotypes, such as familial ectopia lentis. Therefore, a revised Ghent nosology has now been developed to enhance more accurate diagnosis (Table 3). In the revised Ghent diagnostic criteria, greater emphasis has been placed on 2 fundamental features of Marfan syndrome: aortic dilatation and ectopia lentis. Other less specific traits have been combined to comprise a systemic score in which different points are awarded for various characteristics (Table 4). Furthermore, the updated Ghent nosology emphasizes the significance of family history and recommends a separate set of standards for patients with sporadic cases.

Any presence of aortic involvement (by Z score or by rupture/dissection), ectopia lentis, or systemic involvement (≥7 by the scoring system in Table 4) is sufficient to diagnose Marfan syndrome in an individual with strong family history. Thus, family history serves as a potent marker of genetic background in these diagnostic criteria for this mendelian disorder that still obviates the need for genetic testing in most patients with Marfan syndrome. In combina-
tion with these newly revised Ghent criteria, FBN1 genetic testing, although clinically available, is only relevant to the small fraction (likely <5% to 10%) of adults who have no family history of the disorder and do not meet sufficient clinical criteria to definitively establish a diagnosis of Marfan syndrome. From a practical perspective, the management of patients who appear to have a familial aortic aneurysm syndrome that cannot be defined with certainty as Marfan syndrome (or Loeys-Dietz or Ehlers-Danlos syndromes) with or without genetic testing is similar to that of patients with Marfan syndrome.

### Table 3. Revised Ghent Criteria for Diagnosis of Marfan Syndrome

<table>
<thead>
<tr>
<th>Without Family History</th>
<th>With Family History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic dissection or Z score ≥2 + ectopia lentis</td>
<td>Aortic dissection or Z score ≥2 in adults, ≥3 in children or</td>
</tr>
<tr>
<td>Aortic dissection or Z score ≥2 + FBN1 mutations</td>
<td>Ectopia lentis or</td>
</tr>
<tr>
<td>Aortic dissection or Z score ≥2 + systemic score ≥7 points*</td>
<td>Systemic score ≥7 points</td>
</tr>
<tr>
<td>Ectopia lentis + FBN1 mutations with known aortic involvement</td>
<td></td>
</tr>
</tbody>
</table>

*Without discriminating features of Loeys-Dietz, vascular Ehlers-Danlos, or Shprintzen-Goldberg syndrome.

### Modification of Clinical Criteria by Family History in Marfan Syndrome

- In the presence of documented family history, any presence of ectopia lentis, aortic dissection/aneurysm, or systemic score ≥7 points confirms the diagnosis of Marfan syndrome.

### Summary

As shown with these examples of the mendelian cardiovascular disorders, understanding the genetic transmission of a disorder plays a critical role in diagnosing and managing these diseases. Individuals with strong family history of autosomal dominant cardiovascular disease, which raises the a priori likelihood of disease from 1 in 500 to 5000 in the general population to 1 in 2, should be assessed with a different approach in comparison to individuals with sporadic diseases. With all of the aforementioned mendelian disorders, the presence of a strong family history is usually a major diagnostic criterion. Even in the case of HCM, in which there are not established and uniformly accepted diagnostic guidelines, the presence of family history should steer any signs of LVH toward a diagnosis of HCM, and management needs to be guided depending on the presence of malignant phenotype in the family. Because of variable penetrance and expressivity at various ages, serial screening is often necessary even in individuals without any initial manifestation. In the case of such mendelian cardiovascular disorders with potentially malignant and lethal phenotypes, consultation with a specialist expert in the genetic basis, diagnosis, and treatment of the particular disorder should be considered if the diagnosis remains ambiguous under current guidelines. Although the identification of culprit genes has produced significant advances in the field of genetics, cardiovascular genetic testing is still in its infancy and is useful in only limited situations with most of the mendelian cardiovascular disorders. Therefore, involvement of clinicians experienced with all genetic and phenotypic aspects of these disorders may limit unnecessary genetic testing and foster prompt diagnosis. With further progress in the field of genetics, the role of genetic testing will continue to evolve. However, clinical decisions should be made now by incorporating clinical data along with easily available genetic information such as family history for all individuals being evaluated.

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### Disclosures

Dr Kim has no conflicts to disclose. Dr Basson directs cardiovascular translational medicine at the Novartis Institutes for Biomedical Research. Dr Devereux serves on advisory committees related to cardiorenal matters and hypertension for Merck and Novartis.

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