Hypertrophic cardiomyopathy (HCM) is a common monogenetic cardiac disease with a prevalence of 0.2%\(^1\) that usually is inherited as an autosomal dominant trait with variable penetrance and expression. Clinically, HCM is defined by the presence of left ventricular (LV) hypertrophy (LVH) unexplained by abnormal loading conditions.\(^1\) The natural history varies from an asymptomatic course to drug-refractory angina/dyspnea, sudden cardiac death (SCD), and end-stage heart failure. The incidence of HCM-related SCD is approximately 1% to 2% in children and adolescents and 0.5% to 1% in adults.\(^2,3\) In this review, we examine the impact of advanced diagnostic imaging technologies on HCM, with particular emphasis on the detection of particular genetic subtypes.

State-of-the Art in Genetics of HCM

In \(\approx 60\%\) of cases, HCM is inherited as an autosomal dominant trait caused by mutations in genes coding for cardiac sarcomere proteins (Figure 1).\(^4–7\) Mutations in genes encoding Z-disc proteins and proteins involved in calcium regulation account for \(\approx 5\%\) of cases. The absence of sarcomeric gene mutations can be explained by limitations of current mutation detection techniques or mutations in as yet unidentified genes, but in some cases, hypertrophy is caused by other diseases that mimic the phenotype of sarcomeric protein disease. Table 1 lists genetic disorders associated with HCM.

Sarcomere and Z-disc Protein Gene Mutations

More than 600 different sarcomeric gene mutations are reported in patients with HCM.\(^8–16\) The majority are missense mutations, but nonsense, frameshift, and in-frame insertion/deletion mutations also occur. Most mutations are characterized by incomplete penetrance and variable clinical expression likely due to locus heterogeneity and the effect of mutations at different locations within the same gene. Most mutations probably have a dominant negative effect on sarcomere function, but in some cases, haploinsufficiency (ie, only a single functional copy of a gene, the other being inactivated by the mutation) also may be important.

It is suggested that hypertrophy results from reduced contractile function, but studies of myocyte function in patients with mutations in sarcomere protein genes are contradictory. Nevertheless, murine models of sarcomeric mutations show increased calcium sensitivity and altered calcium cycling between sarcomere and sarcoplasmic reticulum. In vitro studies using purified myosin filaments and skinned papillary muscle have reported increased calcium sensitivity of force development that results in impaired ventricular relaxation in vivo.\(^17,18\)

Z-discs are lateral boundaries of the sarcomere that play a fundamental role in mechanical stretch sensing. Several mutations in genes coding for Z-disc proteins have been implicated in HCM, including \(\alpha\)-actinin (mediates the interaction between actin and titin) and telethonin (interacts with muscle LIM protein and titin).\(^19,20\) More recently, melusin, a muscle-specific signaling protein required for compensatory hypertrophy response in the pressure-overloaded heart, also has been implicated.\(^21\) A detailed description of metabolic cardiomyopathies that mimic HCM is described in the later part of this article.

State-of-the-Art in Imaging in HCM

In recent years, a comprehensive approach incorporating multiple imaging modalities has been used to determine mechanisms of symptoms and prognosis and to plan therapy. The utility and limitations of each imaging modality are listed in Table 2; current recommendations for use of different imaging modalities are listed in Table 3.

Assessment of Morphology

LV Geometry

Echocardiography is the initial modality of choice for evaluation of cardiac morphology. Although asymmetrical upper-septal hypertrophy is the most commonly observed morphological pattern (Figure 2A and 2B),\(^22\) midventricular, apical...
(Figure 3A and 3B), posterolateral, concentric, and biventricular hypertrophy also occur. Three-dimensional echocardiography quantifies and characterizes myocardial hypertrophy, LV volumes, LV ejection fraction, and LV mass more accurately than traditional 2D echocardiography.23

Cardiac magnetic resonance (CMR) is especially useful in identifying the varied phenotypic presentations of HCM, particularly when hypertrophy involves the anterolateral free wall24 and apical variant,25 which often are poorly visualized on echocardiography. In 1 study,24 CMR accurately identified HCM missed on echocardiography in 6% of the patients. CMR is the gold standard for measurement of LV mass, which might have some prognostic utility.26 Recently, a high prevalence of apical aneurysms, missed by echocardiography in 43% cases (albeit, without the use of contrast), was demonstrated using CMR.27

Currently, CMR cannot be used in most patients with pacemakers or implanted defibrillators; however, this may change as newer safety data emerge. As an alternative to CMR, cardiac CT can be used for morphological charac-

Table 1. Currently Known Genes Implicated in HCM

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Frequency in Patients With HCM Phenotype</th>
<th>Associated Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarcomeric mutations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MYH7</td>
<td>β-myosin heavy chain</td>
<td>25%–35%</td>
<td>Variable</td>
</tr>
<tr>
<td>MYBPC3</td>
<td>Myosin-binding protein C</td>
<td>20%–30%</td>
<td>Variable, late onset</td>
</tr>
<tr>
<td>TNNT2</td>
<td>Troponin T</td>
<td>3%–5%</td>
<td>Sudden death</td>
</tr>
<tr>
<td>TNNI3</td>
<td>Troponin I</td>
<td>&lt;5%</td>
<td>Extreme heterogeneity</td>
</tr>
<tr>
<td>TPM1</td>
<td>Tropomyosin 1α</td>
<td>&lt;5%</td>
<td>Variable prognosis, sudden death</td>
</tr>
<tr>
<td>MYL2</td>
<td>Regulatory myosin light chain 2</td>
<td>&lt;5%</td>
<td>Skeletal myopathy</td>
</tr>
<tr>
<td>MYL3</td>
<td>Essential myosin light chain 3</td>
<td>Rare</td>
<td>Skeletal myopathy</td>
</tr>
<tr>
<td>ACTC</td>
<td>α-Cardiac actin 1</td>
<td>Rare</td>
<td>Apical hypertrophy</td>
</tr>
<tr>
<td>TTN</td>
<td>Titin</td>
<td>Rare</td>
<td>Typical</td>
</tr>
<tr>
<td>TNNC1</td>
<td>Troponin C, slow skeletal and cardiac muscles</td>
<td>Rare</td>
<td>Typical</td>
</tr>
<tr>
<td>MYH6</td>
<td>α-Myosin heavy chain</td>
<td>Rare</td>
<td>Late onset</td>
</tr>
<tr>
<td>Nonsarcomeric mutations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSRP3</td>
<td>Muscle LIM protein</td>
<td>Rare</td>
<td>Late onset</td>
</tr>
<tr>
<td>MYLK2</td>
<td>Myosin light chain kinase 2</td>
<td>Rare</td>
<td>Early onset</td>
</tr>
<tr>
<td>LDB3</td>
<td>LIM binding domain 3</td>
<td>Rare</td>
<td>Mainly sigmoidal</td>
</tr>
<tr>
<td>TCAP</td>
<td>Telethonin</td>
<td>Rare</td>
<td>Typical, variable</td>
</tr>
<tr>
<td>VCL</td>
<td>Vinculin/metavinculin</td>
<td>Rare</td>
<td>Obstructive midventricular hypertrophy</td>
</tr>
<tr>
<td>ACTN2</td>
<td>α-Actinin 2</td>
<td>Rare</td>
<td>Mainly sigmoidal</td>
</tr>
<tr>
<td>PLN</td>
<td>Phospholamban</td>
<td>Rare</td>
<td>Typical, variable</td>
</tr>
<tr>
<td>MYOZ2</td>
<td>Myozenin 2</td>
<td>Rare</td>
<td>Typical</td>
</tr>
<tr>
<td>JPH2</td>
<td>Junctophilin 2</td>
<td>Rare</td>
<td>Typical</td>
</tr>
</tbody>
</table>
terization and adds the ability to assess coronary artery anatomy.28

**Evaluation of Mitral Valve and Subvalvular Apparatus**
Mitral valve abnormalities are common in HCM. The most frequent is systolic anterior motion (SAM) of the anterior (less commonly posterior) leaflet of the mitral valve in systole, but other structural abnormalities frequently are seen, including calcification of the mitral valve annulus and elongation of 1 or more cusps of either leaflet. Echocardiographic studies also have demonstrated reduced mobility and length of the posterior mitral leaflet, leading to a shorter coaptation length.29 This results in a longer free segment of the anterior leaflet that is susceptible to drag forces, leading to SAM.30 The direction of MR jet is an important clue in identifying the underlying mechanism31 because an anteriorly/medially directed jet is most likely due to primary posterior leaflet pathology, whereas SAM usually results in a posterior jet. Surface and transesophageal echocardiography (TEE) (including 3D) (online-only Data Supplement Movie 1) may be required to understand mitral valvular and chordal anatomy.28

**Evaluation of Myocardial Fibrosis**
Gadolinium-enhanced CMR provides an accurate method for detection of myocardial fibrosis.38 In patients with HCM, myocardial fibrosis is patchy, midmyocardial, and most commonly found in regions of hypertrophy, especially in the interventricular septum at the right ventricular insertion point (Figures 2C and 2D and 3C and 3D). The pattern and amount of fibrosis correlates closely with histopathology39,40 and coronary arteriole dysplasia.40 Fibrosis, defined by CMR, is detectable in 75% to 80% of patients with HCM and correlates with wall thickness and inversely with regional function.41-43

The long-term clinical significance of fibrosis is uncertain. Extent of fibrosis, particularly in patients aged <40 years, is associated with clinical markers of SCD, whereas in older patients, it is associated with progressive ventricular dysfunction.44 Furthermore, studies have demonstrated an association between degree of myocardial fibrosis and ventricular arrhythmia.42,43,45,46 Emerging data demonstrate incremental prognostic value of myocardial fibrosis assessment in pre-
dicting hard outcomes. However, long-term prospective studies establishing the association between fibrosis and SCD are needed.

Functional Assessment

Evaluation of LV Cavity Obstruction

Approximately 70% of patients with HCM with asymmetrical septal hypertrophy have evidence of resting or provokable LV cavity obstruction, which can occur at multiple levels and is dynamic, varying with changes in heart rate, afterload, contractility, and intravascular volume. LVOTO is associated with worse clinical outcomes, including progression to heart failure and death. LVOTO usually is caused by SAM of the mitral valve leaflet. The mechanism is complex but involves narrowing of the LVOT by septal hypertrophy, elongation of mitral leaflets, and anterior displacement of the mitral apparatus and papillary muscles. SAM may be complete, incomplete, or chordal. The location and severity of obstruction is best assessed by pulsed Doppler and continuous-wave Doppler echocardiography, taking care to distinguish the Doppler envelope from mitral regurgitation. Care also should be taken to exclude other causes of LVOTO, including subaortic membrane and accessory mitral valve tissue. Obstruction also occurs at the midcavity level and the ventricular apex. Recently, 3D quantification of LVOT area has been shown to have added utility in the assessment of LVOTO.

Many patients without outflow obstruction at rest develop it during physiological and pharmacological interventions that reduce LV end-diastolic volume or increase LV contractility (eg, amyl nitrate inhalation, Valsalva maneuver, and administration of intravenous inotropic agents). In patients with exertional symptoms, provocative maneuvers are recommended when the resting LVOT gradient is <30 mm Hg. If the resting gradient is >50 mm Hg, then provocation may not be necessary. Valsalva is the simplest maneuver but has low sensitivity, and pharmacological provocation needs to be done with careful imaging to ensure that the observed Doppler signal is not due to cavity obliteration. However, neither Valsalva nor pharmacological stress reliably reproduce the physiological circumstances in which latent obstruction is likely to occur, and gradients produced during such maneuvers correlate poorly with those induced by exercise. Consequently, exercise stress echocardiography is now the preferred method for provoking gradients. The safety of exercise stress echocardiography has been established previously. It provides crucial information about exercise-induced LVOT gradient, functional capacity, and blood pressure response to exercise. In very few patients, low-dose infusions of isoproterenol in conjunction with real-time 2D assessment for SAM and dynamic LVOTO, using TEE is necessary. Identifying and treating provokable obstruction results in significant overall improvement in patients with HCM.

Phase velocity flow mapping on CMR also can be used to determine the peak LVOT velocity. One study demonstrated the feasibility of identifying patients with obstructive physiology based on the LVOT area measured by CMR. However, because of many technical limitations of CMR, Doppler echocardiography remains the method of choice for determining LVOT gradients in clinical practice.

Evaluation of Systolic and Diastolic LV Function

Multiple mechanisms, including hypertrophy, myocyte disarray, fibrosis, and abnormal calcium metabolism, contribute to diastolic dysfunction. Integrated assessment of several echocardiographic diastolic indices, including pulmonary vein
Flow, tissue Doppler imaging, and transmitral inflow, can provide reasonably accurate predictions of filling pressures. E/Ea ratio correlates weakly with exercise capacity, and changes in E/Ea ratio have been demonstrated after alcohol septal ablation and cardiac surgery. Septal Ea is an independent predictor of death and ventricular dysrhythmia in children with HCM. Although these observations have been made in smaller cohorts, larger cross-sectional studies have failed to significantly correlate Doppler filling patterns, extent of LVH, and invasive indexes of diastolic function.

**Figure 2.** A 27-year-old man with HCM. A, Two-dimensional echocardiographic image demonstrating asymmetrical basal septal hypertrophy. B, Doppler across the LVOT demonstrating the late-peaking gradient. C, Cine CMR image confirming severe septal hypertrophy. D, Delayed hyperenhancement CMR image demonstrating fibrosis in the hypertrophied septum.

**Figure 3.** A 35-year-old man with HCM. A, Two-dimensional echocardiographic image demonstrating severe apical hypertrophy. B, Doppler measurement across the LVOT demonstrating absence of obstruction. C, Two-chamber cine CMR image confirming severe apical hypertrophy. D, Delayed hyperenhancement CMR image demonstrating fibrosis in the hypertrophied myocardium.
Although assessment of systolic function generally is performed by measuring LV ejection fraction (which can be measured by different imaging techniques), it does not reflect the true systolic function in HCM. CMR studies have demonstrated reduced circumferential shortening in hypertrophied segments that was inversely related to local thickness, with most shortening occurring in early systole.62,63 Another recent study demonstrated reduced LV strain (measured by speckle tracking echocardiography) in patients with HCM, even in the absence of fibrosis. Myocardial fibrosis was associated with further reduction in longitudinal strain.64

**Ventricular-Vascular Interactions**

It was demonstrated recently that LVOT and aortic root are oriented at a steeper angle to the LV in patients with HCM versus normal controls65 and that the angle is independently associated with maximal LVOT gradient. Recently,66 pulse-wave velocity using phase-contrast CMR demonstrated stiffer aortas in patients with HCM versus controls and that aortic stiffness was greater in patients with HCM with myocardial fibrosis versus those without. Further work has demonstrated that aortic stiffness is associated with exercise capacity independent of LV morphology, diastolic function, and LVOT gradients.67

**Risk Stratification for SCD**

SCD is a relatively uncommon, but catastrophic complication of HCM, often occurring during mild-moderate exertion.1,2,4,68–71 A thorough history (including extended family history), physical examination, and imaging evaluation are essential to determine SCD risk. Maximal LV thickness $\geq$ 3 cm is a major risk factor for SCD.2,70 LVOT gradients $>30 \text{ mm Hg}$ have been associated with increased risk of SCD, progression to heart failure, arrhythmia, and stroke.49,72 However, the variable nature of LVOT gradients represents a significant limitation to its use as a risk marker of SCD. Other major risk factors include an abnormal blood pressure response during exercise,53 nonsustained ventricular tachycardia, unexplained syncope, and a family history of premature SCD. Previous data from CMR studies have suggested an association between myocardial fibrosis and ventricular arrhythmia.62,43,45,46 Additionally, emerging data demonstrate incremental prognostic value of myocardial fibrosis assessment in predicting hard outcomes.47,48

The role of genetic analysis in risk stratification remains controversial. MYH7-R403Q mutation was associated with increased mortality, whereas a neutral substitution (V606M) was associated with normal survival.73 Early data on the clinical expression from MYBPC mutation indicated a later onset and milder disease74 and that mutations in TNNT2 (troponin T) were associated with less severe hypertrophy and fibrosis but severe disarray and a higher incidence of SCD.75,76 More recently, a larger study has shown an increased risk of composite cardiovascular events with a positive HCM genetic test involving any sarcomeric genes compared with patients with a negative test.77 Additionally, patients with multiple mutations, detected in about 3% to 5% of genotype-positive patients, had a more severe phenotype and increased incidence of SCD.78,79 However, family studies show that expression of mutations is heterogeneous, even between individuals within families. Further, the majority of diseases causing mutations are rare, making it difficult to determine the SCD risk associated with particular genetic variants in an adequate number of patients. For these reasons, detection of specific mutations is insufficient to implant an implantable cardioverter defibrillator in the absence of other major risk factors.

**Clinical and Imaging-Based Differential Diagnosis of HCM**

In routine clinical practice, a systematic approach to the assessment of family pedigree, symptoms, and physical examination in combination with a detailed imaging evaluation and, in some cases, biochemical testing, is central to differential diagnosis of HCM. In some patients, there may be clinical clues that suggest a particular etiology (eg, facial dysmorphia in Noonan syndrome). There also may be clues on the ECG (ventricular preexcitation in storage diseases and mitochondrial disorders). There are few, if any, disease-specific changes on echocardiography, but in context, a number of features can point to possible diagnoses. For example, concentric hypertrophy tends to be more common in metabolic and storage disorders than in patients with sarcomeric gene mutations. Similarly, bialtrial dilatation, restrictive physiology, and an abnormal texture of the interventricular septum (granular sparkling) should suggest amyloidosis. Recently, it has been suggested that septal morphology is preferentially sigmoidal in patients with Z-disc mutations in contrast to myofilament HCM, which generally has a reverse septal curvature.80

**Metabolic Cardiomyopathies**

In <10% of infants and children and an even smaller proportion of adults, HCM is caused by inborn errors of metabolism, neuromuscular disorders, and malformation syndromes. Anderson-Fabry disease is an X-linked lysosomal storage disorder caused by mutations in the $\alpha$-galactosidase A gene that causes progressive accumulation of glycosphingolipid in various organs, including the heart. Cardiac manifestations include progressive wall thickening (Figure 4), valve disease, conduction abnormalities, and arrhythmias. Disease expression typically begins after adolescence.81 Danon disease, an X-linked lysosomal storage disorder caused by mutations in the gene encoding the lysosome-associated membrane protein 2,82 is characterized by cardiomyopathy, skeletal myopathy, and developmental delay. Other features include Wolff-Parkinson-White syndrome, elevated serum creatine kinase, and retinitis pigmentosa. Males develop symptoms during childhood and adolescence, whereas females develop cardiomyopathy during adulthood. The prognosis is poor, with most patients dying from cardiac failure, although SCD is reported.

Pompe disease is an autosomal recessive disorder caused by a deficiency in the lysosomal enzyme acid maltase. The infantile form presents in the first few months, with severe skeletal muscle hypotonia, cardiomyopathy, hepatomegaly, and macroglossia, and usually is fatal before 2 years without treatment. Mutations in the gene encoding the $\gamma_2$
subunit of the AMP-activated protein kinase (PRKAG2) cause a syndrome of HCM, conduction abnormalities, and Wolff-Parkinson-White syndrome.83 Respiratory chain disorders (mitochondrial cardiomyopathies) are caused by sporadic or inherited mutations in nuclear or mitochondrial DNA transmitted as autosomal dominant, recessive, X-linked, or maternal traits.84 These disorders vary in age at onset, symptoms, and range and severity of organ involvement. The phenotype usually is concentric LVH without outflow tract obstruction, often with rapid progression to LV dilatation and heart failure.

Noonan syndrome is characterized by short stature, facial dysmorphism, skeletal malformations, and a webbed neck.22 Cardiac involvement is present in up to 90% of patients (pulmonary valve stenosis and HCM). It is inherited as an autosomal dominant trait with variable penetrance and expression. Mutations in \( \text{PTPN11} \) gene, encoding the protein tyrosine phosphatase SHP-2, account for \( \approx 50\% \) of cases, but only 5% to 9% of all individuals with mutations in the \( \text{PTPN11} \) gene have HCM.85 LEOPARD (lentigines, ECG abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, growth retardation, and deafness) syndrome shares many features with Noonan syndrome and is also caused by mutations in the \( \text{PTPN11} \) gene.23 Noonan syndrome and LEOPARD syndrome are examples of neurocardio-facial-cutaneous syndromes. Many are caused by germline mutations in key components of the highly conserved RAS-MAPK cascade.86 Missense \( \text{PTPN11}, \text{KRAS}, \text{SOS1}, \text{RAFI}, \text{MEKI}, \) and \( \text{BRAF} \) gene mutations have been associated with HCM.

**CMR and Different Cardiomyopathies**

Some patterns of myocardial late-gadolinium enhancement on CMR have been reported more frequently in particular cardiomyopathies, for example, midmyocardial posterolateral scarring in the LV (Fabry disease in Figure 4D, glycogen storage disease)87 and diffuse myocardial pattern in cardiac amyloidosis.88 However, these patterns are not specific and must be interpreted in light of the clinical presentation.

**Hypertensive Heart Disease**

A common clinical dilemma is the diagnosis of HCM in patients with hypertension. Hypertension typically produces concentric remodeling of the LV rather than asymmetrical hypertrophy. Moderate to severe hypertrophy (\( \geq 15 \) mm) is rare in whites with mild to moderate hypertension, and the presence of a family history of cardiac hypertrophy in a nonhypertensive relative or a positive gene test increases the likelihood of HCM. SAM and LVOTO are recognized but are less common in hypertensive heart disease. Finally, in hypertension but not HCM, treatment with antihypertensives can regress LVH. Recently, deformation imaging has been shown to distinguish between patients with HCM and those with hypertension.89 In one of the earliest efforts to discern the morphology of HCM, the septal contour was divided into reverse curvature, sigmoid shape, apical predominance, and concentric, although observing that the sigmoid shape was more predominant in elderly patients with hypertensive heart disease90 and that this sigmoid shape was less likely to be the result of an underlying sarcomeric mutation.91

**Athlete’s Heart**

Differentiation of physiological hypertrophy from HCM in elite athletes also can pose a problem, but in many cases, analysis of ECG, echocardiography, and CMR facilitates accurate diagnosis (Figure 5).92,93 In athletes’ hearts, LV cavities are typically enlarged, wall thickness is usually \( < 15 \) mm, and myocardial fibrosis is absent. In contrast,
patients with HCM usually have normal or reduced LV dimensions and no cavity dilatation (> 55 mm common in athletes), except with disease progression and systolic dysfunction. In borderline cases, it is reasonable to recommend the cessation of exercise with repeat imaging in order to detect regression of physiological LVH.

State-of-the-Art Imaging in Therapeutic Decision Making in HCM

In a symptomatic patient with HCM, the goal of imaging is to characterize the mechanism of obstruction and the feasibility of different therapeutic interventions. Although 2D echocardiography (and in some cases TEE) are sufficient, 3D echocardiography and CMR are rapidly emerging as useful adjuncts, especially for assessment of mitral valve and papillary muscle morphology. In patients with LVOTO and septal hypertrophy that is not significant (typically <1.8 cm), an extensive myectomy would not be indicated. In such cases, alternate surgical options, such as mitral valve repair/replacement and papillary muscle reorientation, need to be considered in addition to a minimyectomy (≤5 mm muscle removal). Figure 6 demonstrates the different potential therapeutic approaches based on septal thickness, mitral valve, and papillary muscle pathology.

After the decision has been made to proceed with surgery, intraoperative TEE plays an invaluable role because it helps to estimate the amount of myocardium that needs to be removed and the length of the anterior mitral leaflet. It is also important after surgery to determine whether residual SAM, LVOTO (measured either directly or with isoproterenol

Figure 5. A 17-year-old subject with an athlete’s heart. A, Two-dimensional echocardiographic image demonstrating absence of LVH. B, Doppler measurement demonstrating normal diastology. C, Four-chamber cine CMR image confirming absence of LVH. D, Delayed hyperenhancement CMR image demonstrating no fibrosis.

Figure 6. Potential schemata for management of symptomatic patients with significant LVOTO. ASA indicates alcohol septal ablation; MV, mitral valve; PM, papillary muscle; PMR, papillary muscle reorientation.
provocation), and MR are present, which may necessitate further intervention. On the other hand, if the decision is made to proceed with alcohol septal ablation, contrast echocardiography provides essential procedural guidance by identifying the myocardial territory perfused by the target vessel.\(^96\) Contrast opacification beyond the area of the basal anteroseptum precludes ethanol injection. CMR also can be used to assess the degree and unpredictable nature of septal regression after alcohol ablation.\(^97\) In addition, fibrosis assessment by CMR might have a future role in risk stratification, especially when there is clinical uncertainty about whether to recommend a defibrillator.

### Screening: Family Members and Asymptomatic Individuals

Because HCM is a genetic disorder in many cases, relatives of an index case (proband) can be at risk for developing the disease. The primary aim of family screening, therefore, is to identify relatives who have the same disease as the proband in order to prevent complications and inform life choices. In some cases, assessment of the family also may assist in diagnosing a borderline clinical phenotype.

There generally are 2 approaches to family screening. The first is a clinical strategy based on the use of simple noninvasive tests, such as an ECG and echocardiogram. In addition to standard echocardiography, tissue Doppler echocardiography has shown reduced myocardial Doppler velocities in genotype-positive subjects without LVH.\(^98\)–\(^100\) Tagging by CMR also may have a role in early detection of diastolic dysfunction or morphological changes (prehypertrophic crypts), where LVH has not yet manifested.\(^101\),\(^102\) In a recent study, high levels of serum C-terminal propeptide of type I procollagen (even before presence of overt fibrosis on CMR) were demonstrated in subjects with HCM mutations without LVH compared with controls.\(^103\) If a relative has tests consistent with the suspected clinical diagnosis, then screening can be offered to other first-degree relatives (cascade or stepwise screening). A limitation of this approach is that most genetic forms of HCM have age-related penetrance (ie, the HCM phenotype develops during adolescence and adult life), which means that normal clinical tests cannot exclude future risk of disease development and must be repeated at regular intervals throughout life.

An alternative strategy is to identify the causative genetic abnormality in the proband and then offer genetic testing to relatives at risk of developing disease.\(^104\),\(^105\) The advantage of this approach is that relatives who do not carry the mutation can be spared from further clinical screening, whereas those with the mutation can be monitored and advised appropriately. In practice, both strategies are necessary in particular circumstances. For example, when molecular screening fails to identify a mutation or demonstrates a genetic variant of uncertain significance, clinical evaluation of family members should still be considered.

A suggested schema, incorporating genetic and clinical screening, based on the current guidelines and position statements is shown in Figure 7.\(^104\),\(^105\) There are a couple caveats that need to be considered. First, in a gene-negative first-degree relative of a gene-positive proband (who has multiple risk factors for SCD), it might be prudent to consider imaging in that relative, irrespective of the genotype status. Second, imaging generally is more readily (and in most cases, rapidly) available than genetic testing. It might be prudent to perform cardiac evaluation (including ECG and echocardiography) in all first-degree relatives of the gene-positive proband while waiting for the results of the genetic test. Follow-up imaging in such circumstances could be dictated by the results of the genetic test, as outlined in Figure 7.

### Conclusions

Improved cardiac imaging and advances in our understanding of a genetic basis for HCM have dramatically increased our ability to diagnose and manage patients with HCM. In the future, integration of structural and functional information with detailed
molecular analysis will provide the basis for new therapeutic interventions that improve quality of life and protect patients and families from disease-related complications.

Disclosures

None.

References


Keywords: cardiomyopathy ■ hypertrophy ■ imaging ■ genetics
Imaging Phenotype Versus Genotype in Hypertrophic Cardiomyopathy
Milind Y. Desai, Steve R. Ommen, William J. McKenna, Harry M. Lever and Perry M. Elliott

*Circ Cardiovasc Imaging*. 2011;4:156-168
doi: 10.1161/CIRCIMAGING.110.957936
*Circulation: Cardiovascular Imaging* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/4/2/156

Data Supplement (unedited) at:
http://circimaging.ahajournals.org/content/suppl/2011/03/17/4.2.156.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation: Cardiovascular Imaging* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation: Cardiovascular Imaging* is online at:
http://circimaging.ahajournals.org//subscriptions/