

THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Diagnosis and Evaluation of Hypertrophic Cardiomyopathy



JACC State-of-the-Art Review

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ABSTRACT

Hypertrophic cardiomyopathy (HCM) is a relatively common often inherited global heart disease, with complex phenotypic and genetic expression and natural history, affecting both genders and many races and cultures. Prevalence is 1:200-1:500, largely based on the disease phenotype with imaging, inferring that 750,000 Americans may be affected by HCM. However, cross-sectional data show that only a fraction are clinically diagnosed, suggesting under-recognition, with most clinicians exposed to small segments of the broad disease spectrum. Highly effective HCM management strategies have emerged, altering clinical course and substantially lowering mortality and morbidity rates. These advances underscore the importance of reliable HCM diagnosis with echocardiography and cardiac magnetic resonance. Family screening with noninvasive imaging will identify relatives with the HCM phenotype, while genetic analysis recognizes preclinical sarcomere gene carriers without left ventricular hypertrophy, but with the potential to transmit disease. Comprehensive initial patient evaluations are important for reliable diagnosis, accurate portrayal of HCM and family history, risk stratification, and distinguishing obstructive versus nonobstructive forms.

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INTRODUCTION

Once considered a rare inherited cardiac disease, difficult to diagnose and without effective management options, HCM is now recognized as much more common with worldwide distribution (Figure 1), with a general population prevalence of 1:200-1:500, and effective treatment interventions that have significantly reduced disease-related mortality and morbidity.^{1,2} As a consequence, reliable identification and detailed clinical assessment for patients and

family members, as well as a high index of diagnostic suspicion have increased substantially in importance.

The development of modern cardiovascular imaging with echocardiography >50 years ago has had a particular affinity for HCM, given its diverse morphologic expression that can prove challenging to clinicians, especially those unfamiliar with its broad disease spectrum. For example, the HCM phenotype encompasses patients with differing magnitude of left ventricular (LV) mass, eg, from mild LV wall thickness (≤ 15 mm) to massive hypertrophy ≥ 30 mm



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HIGHLIGHTS

- HCM has a prevalence of 1:200-1:500 in the population, but a minority of cases (10%-20%) are identified clinically.
- HCM is treatable and consistent with normal longevity, making timely, accurate diagnosis a priority.
- Echocardiography and CMR are synergistic for diagnosis in probands and family screening, and genetic testing can identify affected individuals without the HCM phenotype.

(arguably the most substantial of any cardiac disease), as well as gene carriers in whom LV hypertrophy is absent.³⁻⁵ Imaging markers also contribute to selection of patients for prevention of sudden death with implantable defibrillators. Because uncertainties may remain regarding the roles of genetic analysis and cardiac magnetic resonance (CMR) for diagnosis and management, a consortium of experts has been assembled for the purpose of making recommendations regarding the most contemporary principles for patients with this complex disease.

THE JACC EXPERT PANEL

The Expert Panel comprised solely clinicians and thought leaders, each with highest level of personal experience with HCM from major centers dedicated to this disease. This unique consensus document was the product of a systematic overview approach producing evidence-based recommendations and insights that reflect extensive practice experience (cumulative, 250 years) derived from direct interactions with HCM patients over decades, as well as knowledge acquired from personal research, and the peer-reviewed literature.

It was our goal to create a concise but comprehensive best care model emphasizing decision pathways for HCM scenarios commonly encountered in clinical practice, with reliance on the most up-to-date literature (including 2021), and the progress made in the diagnosis and treatment. We also wish to underscore that a disease such as HCM may not lend itself readily to rigid guideline-type categorizations that do not adequately capture the complexity of this particular disease, or the realities of clinical practice.⁶⁻⁸ Therefore, we have expressed key principles for HCM in “real-world” clinical language. The flexibility afforded by the present

state-of-the-art format represents a distinct advantage in this regard.

The present expert and evidence-based recommendations offer ease of interrogation to identify decision-making principles that can be applied while not restraining the diagnosis or management of individual patients. Although panel members support (and promote) the advantages of specialized and dedicated multidisciplinary HCM referral center programs as models of care,^{1,6,7} an equally important objective is to more expansively inform cardiovascular practitioners caring for most HCM patients in general cardiology environments outside of referral centers. Furthermore, we recognize that no set of recommendations can fully embrace all conceivable clinical scenarios and management decisions encountered in a disease such as HCM, and implementation of contemporary strategies may not yet be available for each and every patient, or in all venues.

Our recommendations allow for personal preferences and active participation of fully informed HCM patients, in conjunction with physician judgment (based on knowledge, experience, acumen, and intuition) to resolve by medical reasoning ambiguities that inevitably surround decisions for a nuanced disease like HCM, which unavoidably rely largely on observational and nonrandomized data.

INITIAL AND FOLLOW-UP EVALUATIONS

BACKGROUND. In HCM, clinical assessment and management decisions are almost always made in outpatient settings ([Central Illustration, Table 1](#)). Most patients present initially to practicing cardiologists, pediatricians, or internists in the local community often suspected or diagnosed with HCM due to symptom onset, heart murmur, abnormal electrocardiography (ECG), family screening, or imaging unrelated to HCM. Increasingly, it is recognized that patients benefit from referral to dedicated multidisciplinary HCM programs staffed by cardiologists and cardiac surgeons familiar with and actively engaged in HCM management and outcomes research.

The initial comprehensive HCM evaluation prioritizes the following: diagnosis with assessment of LV morphology and function, symptom severity, sudden death risk, family history, lifestyle modification, and a surveillance plan. This visit customarily includes physical examination and targeted personal and family history, in addition to comprehensive noninvasive testing ([Central Illustration, Table 1](#)).

ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

AHA = American Heart Association

CMR = cardiac magnetic resonance

HCM = hypertrophic cardiomyopathy

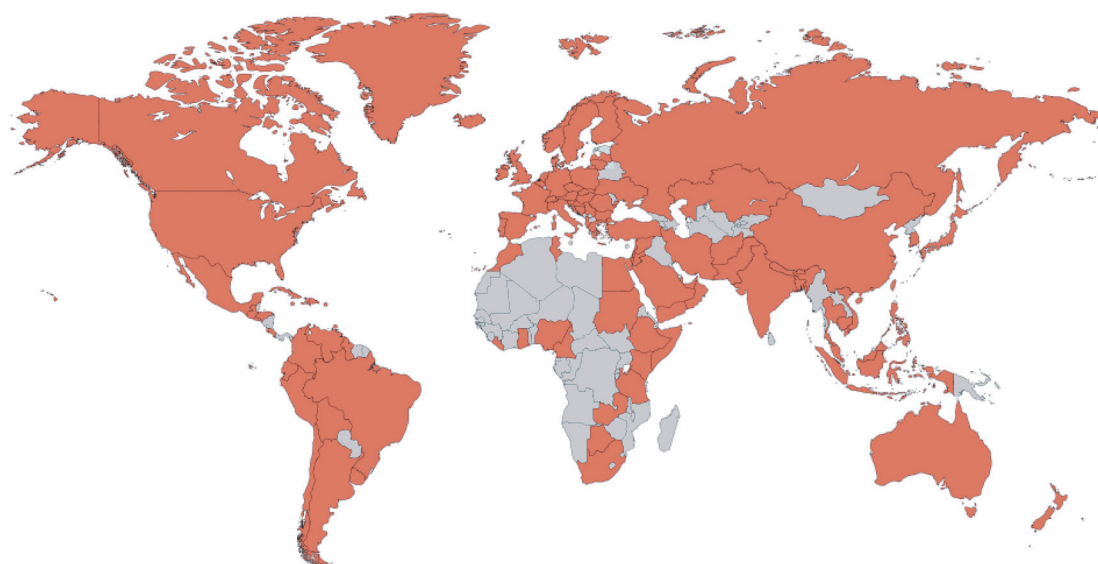
HF = heart failure

ICD = implantable cardioverter-defibrillator

LGE = late gadolinium enhancement

LV = left ventricle/ventricular

LVH = left ventricular hypertrophy

FIGURE 1 Global Distribution of HCM

125 Countries involving 90% of world population

Prevalence
1:200-1:500

Estimated ~15-20 million
affected worldwide

World map showing 125 countries with clinically recognized hypertrophic cardiomyopathy (HCM) (red) and estimated prevalence. Reproduced with permission from Maron et al.¹⁹

CLINICAL PROFILES. It is useful to evaluate patients in the context of specific personalized clinical profiles (subject to evolution over time) (Figure 2)^{1,9-12}: 1) stable benign clinical profile without need to recommend a major treatment intervention^{1,9,10}; 2) LV outflow obstruction with significant heart failure (HF) symptoms, as potential candidates for invasive septal reduction intervention to abolish subaortic gradient and reverse heart failure¹³⁻¹⁷; 3) increased arrhythmic sudden death risk with consideration for an implantable cardioverter-defibrillator (ICD)^{18,19}; 4) atrial fibrillation and risk for embolic stroke with indication for anticoagulation²⁰; and 5) nonobstructive end-stage phase with consideration for advanced HF therapies.^{21,22} Only 10% of HCM patients experience more than 1 of these adverse pathways.

Comprehensive patient-oriented literature designed for HCM patients is available.²³

GUIDE TO CLINICAL MANAGEMENT.

Initial comprehensive evaluation:

- 1. Because a recent HCM diagnosis is typically encumbered by considerable anxiety or confusion, education and prudent reassurance regarding the disease is paramount. The interview should include the relevant principle that in most patients HCM is now a treatable disease compatible with normal longevity.**
- 2. Personal history should focus on: symptoms such as exertional dyspnea or fatigue, syncope, chest pain, prolonged palpitations, family history of affected relatives and HCM-related adverse**

events including sudden death, and significance of LV outflow obstruction (if relevant).

- 3. The following should be established: LV morphology, stratification of sudden death risk, nonobstructive versus obstructive forms, strategy for family screening, and future follow-up.**
- 4. On initial comprehensive evaluation, testing optimally can include echocardiography, 12-lead ECG, ambulatory ECG monitoring (via Holter or wireless patch), contrast cardiac magnetic resonance (CMR), exercise (stress) echocardiography to provoke outflow gradient if absent or mild at rest, and possibly genetic testing.**

Follow-up surveillance:

- 5. Routine re-evaluation is recommended at about 12-month intervals (or up to 24 months based on individual patient profile) to reassess LV morphology, HF symptoms, atrial fibrillation episodes, development of LV outflow obstruction, decrease in ejection fraction, or change in sudden death risk profile. These intervals could be shorter in pediatric patients.**
- 6. Noninvasive testing is dictated by clinical findings but usually includes echocardiogram and 12-lead ECG (every year) and ambulatory ECG monitoring (every 1-3 years). In select patients, contrast CMR may be repeated every 3-5 years, or possibly earlier depending on clinical circumstances.**

Many patients will benefit from referral to multidisciplinary HCM centers, although follow-up care should be coordinated with the local (referring) cardiologist.

NONINVASIVE TESTING

The heterogeneous morphologic and functional expression of HCM is evidenced by imaging with echocardiography and CMR.

DIAGNOSIS. Echocardiography and CMR are established imaging strategies for clinical HCM diagnosis, based on a hypertrophied nondilated LV unassociated with another cardiac, metabolic, or systemic (syndromic) disease capable of producing a similar magnitude of hypertrophy, and with either a disease-causing sarcomere mutation or unresolved genetic etiology (**Figure 3**).^{1,6-8,24} In most age groups, maximum LV thickness ≥ 15 mm at any site in the chamber is consistent with identification of HCM; 13 to 14 mm can be diagnostic, particularly when associated with HCM family history, typical dynamic outflow obstruction, or distinctly abnormal ECG patterns,²⁵

although normal LV wall thicknesses occurs in some genetically affected individuals.²⁶ Average maximal LV thickness (usually ventricular septum) reported in adult HCM populations has historically been 21-22 mm,³⁻⁵ although somewhat less in more recent referral center surveys.²⁵

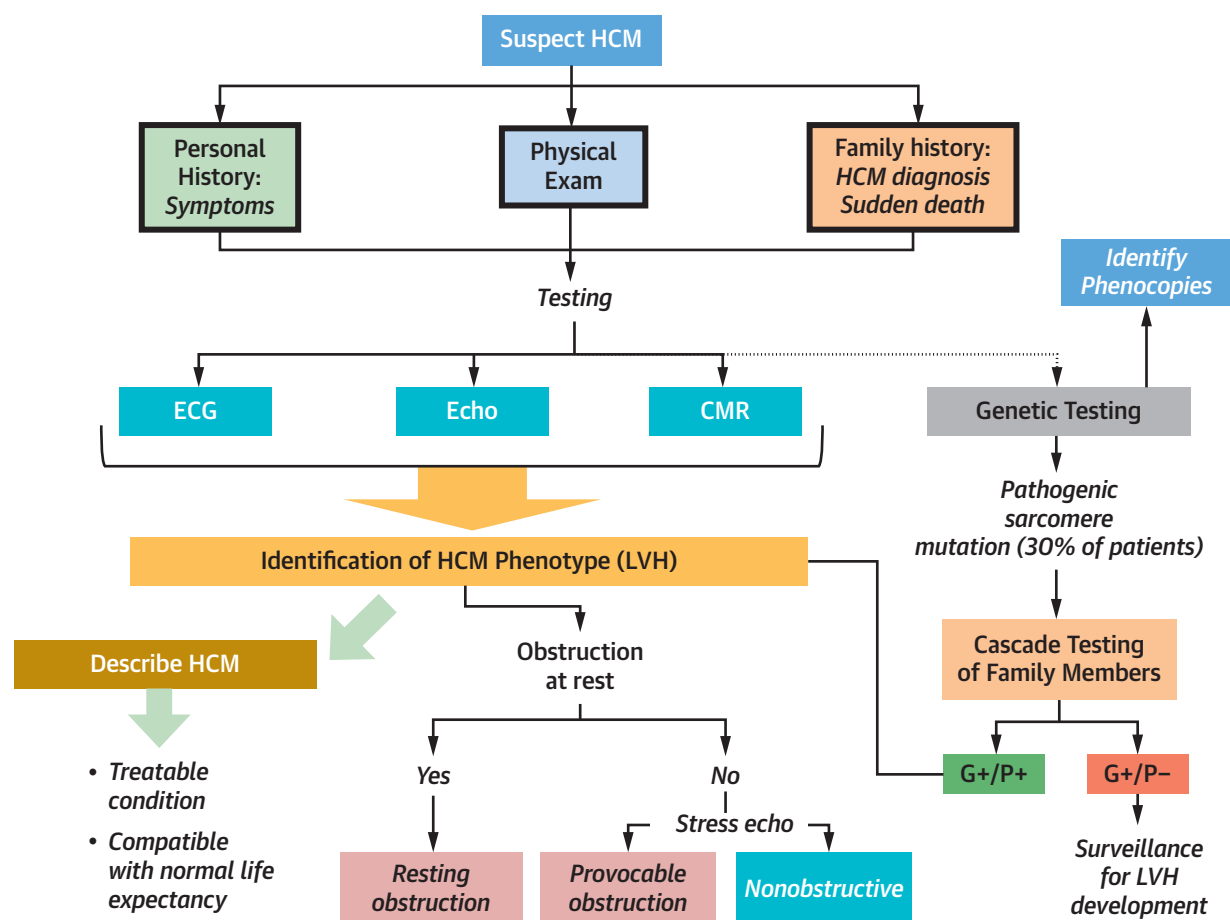
In young children, phenotypic diagnosis depends on LV thickness ≥ 13 mm or distinctly abnormal z score.²⁷ Diverse presentations that expand the broad disease spectrum and deviate from the basic morphologic HCM definition include end-stage HF with remodeling and mild (or no), LV hypertrophy associated with enlarged ventricular chambers,²² and gene carriers without hypertrophy.^{26,28}

A myriad of usually asymmetric patterns of left ventricular hypertrophy (LVH) have been recognized, ie, diffuse involvement of ventricular septum and free wall, but also segmental usually confined to the basal anterior septum or the distal [apical] chamber.^{4,5} Although LV thickness is usually unchanged throughout adulthood, it can be dynamic, increasing in asymptomatic adolescents and young adults, or regressing with progressive evolution to end-stage HF.²²

The major advantage of echocardiography lies with its capability to characterize systolic anterior motion (with mitral-septal contact) and mechanical impedance, as well as other mechanisms of LV outflow obstruction including muscle in the mid-cavity. Echocardiography provides reliable quantitative estimates of peak instantaneous LV outflow gradient, characterizes the magnitude of mitral regurgitation, provides assessment of aortic and mitral valve abnormalities (eg, marked elongation, prolapse, calcification, flail), and estimates systolic pulmonary pressures.

OUTFLOW OBSTRUCTION. Subaortic gradients are reliably estimated with continuous wave echo-Doppler at rest or with exercise, careful to avoid contamination by the mitral regurgitation jet. Amyl nitrite is not widely available for provocation, although the Valsalva maneuver is useful in identifying gradients in patients for whom accurate noninvasive estimation with exercise is not possible. Stress (exercise) echocardiography is an important test in HCM with the capability of provoking labile physiologic LV outflow gradients and is preferable to pharmacologic provocation with amyl nitrite inhalation, or selectively isoproterenol or dobutamine infusion (**Figure 4**).^{3,29} However, invasive hemodynamic assessment with simultaneous pressure tracings can provide information about the outflow gradient in a small proportion of patients, such as when imaging studies are technically unsatisfactory or ambiguous in this regard.

CENTRAL ILLUSTRATION Recommendations for Initial Clinical Evaluation and Testing Algorithm for Patients With or Suspected of Having Hypertrophic Cardiomyopathy



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Evaluation of the HCM patient requires, in addition to targeted personal and family history and physical examination, noninvasive testing to define hemodynamic and clinical subgroups, as well as the identification of gene carriers. CMR = cardiac magnetic resonance; G = genotype; ECG = electrocardiography; echo = echocardiography; HCM = hypertrophic cardiomyopathy; LVH = left ventricular hypertrophy; P = phenotype; SAM = systolic anterior motion.

TABLE 1 Guide to Clinical Evaluation and Noninvasive Testing in HCM

Test	Initial Evaluation	Follow-Up
History taking and examination	+	Annual
Echocardiogram	+	Annual
Contrast CMR ^a	+	Every 3-5 y ^b
Stress (exercise) echocardiography ^c	+	Individualized
Ambulatory ECG ^d	+	1-3 y ^e
12-lead ECG	+	Annual

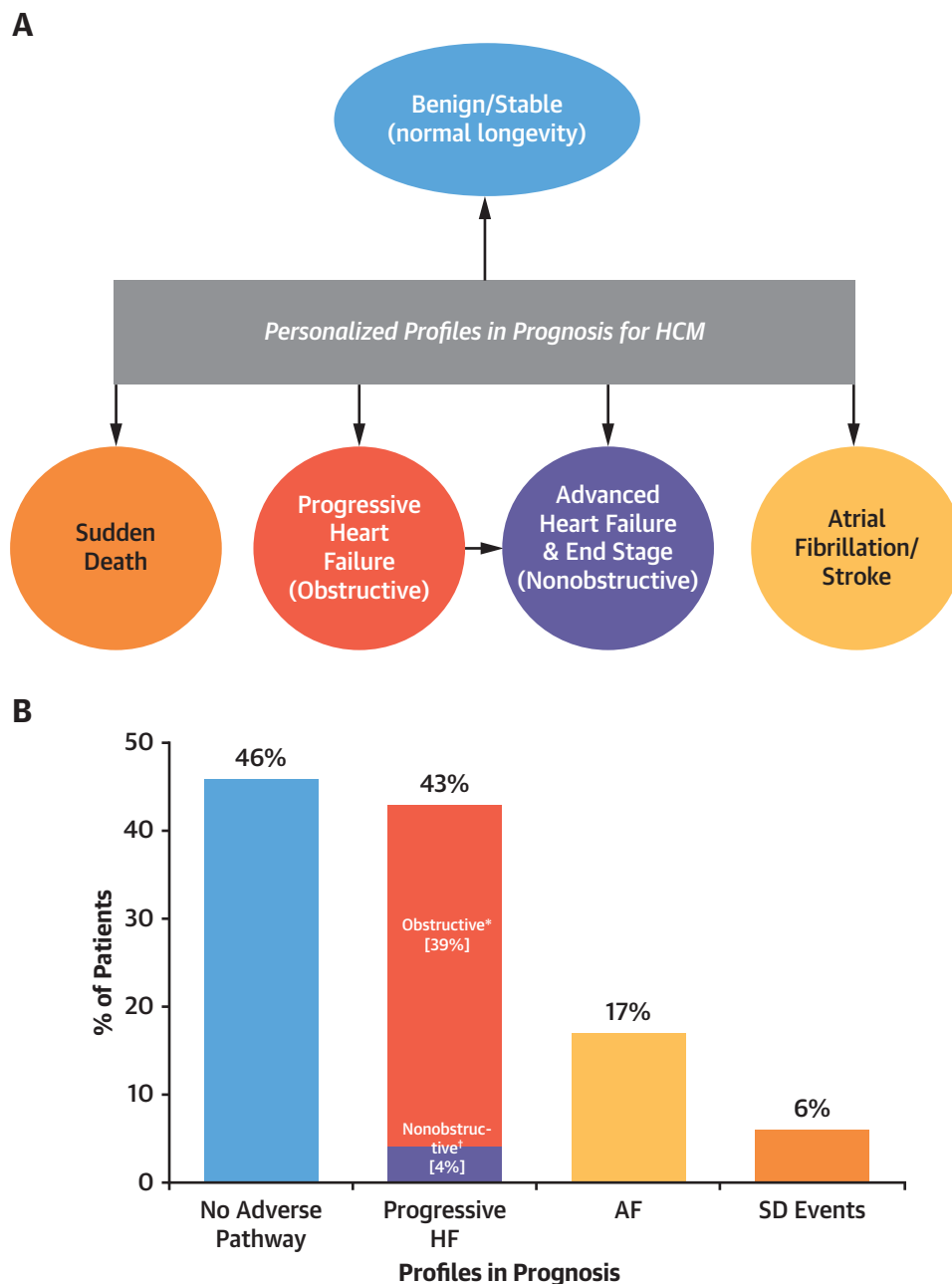
^aOptional in patients >65 years of age. ^bOr more frequently when there is concern for increased late gadolinium enhancement or development of suspected left ventricular apical aneurysm in adults, or increasing wall thickness in young patients. ^cWhen gradient at rest is absent or <30 mm Hg. ^dA 24- to 48-hour Holter or ≥2-week wireless patch with continuous recording. ^eBased on presence or absence of arrhythmia.

CMR = cardiac magnetic resonance; ECG = electrocardiography.

Provoked gradients >30 mm Hg provide prognostic information including prediction of future HF progression from New York Heart Association functional class I or II to class III (at a rate of 3% per year), and also distinguish patients with labile obstruction eligible for invasive relief of the gradient versus non-obstructive candidates for heart transplantation.²⁹

In patients with postprandial dyspnea, exercise testing performed shortly after a modest meal to provoke obstruction can be informative. For those patients incapable of adequate exercise performance, the Valsalva maneuver can serve as a surrogate test to identify provokable obstruction when outflow velocities exceed 3 m/s. Abnormal LV global

FIGURE 2 Clinical Profiles and Prognostic Pathways Across the Expansive HCM Clinical Spectrum

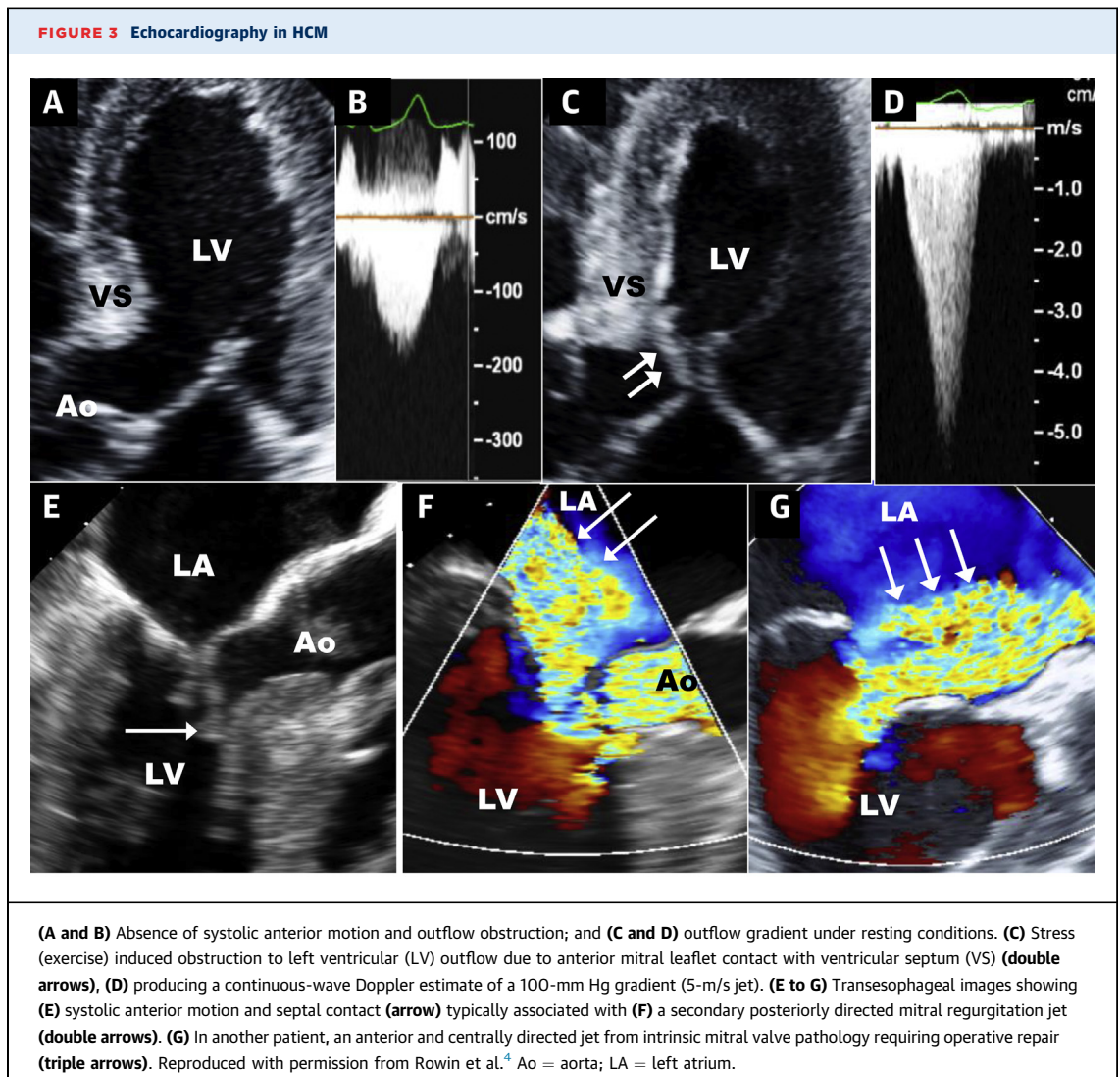


(A) Individual patients may progress along 1 or more of these disease pathways, but along 2 or 3 pathways in only 10% of patients. Alternatively, many hypertrophic cardiomyopathy (HCM) patients experience a benign and stable course without requiring major interventions. **(B)** Frequency of personalized HCM pathways in a 1,000-patient cohort.⁹ *Symptomatic obstructive patients are candidates for surgical myectomy (or selectively alcohol septal ablation); †much less commonly, symptomatic nonobstructive patients can be candidates for heart transplantation. Reproduced with permission from Rowin et al.⁹ AF = atrial fibrillation; HF = heart failure; SD = sudden death.

longitudinal strain has the potential to predict HF progression and LV systolic dysfunction in non-obstructive patients, particularly when combined with conventional ejection fraction.^{30,31} Care is required in distinguishing Doppler outflow profiles

from mitral regurgitation, and to exclude coexistent subaortic membranes.

CONTRIBUTION OF CMR. High spatial and temporal resolution and quantitative contrast CMR is now an integral part of HCM patient assessment in centers

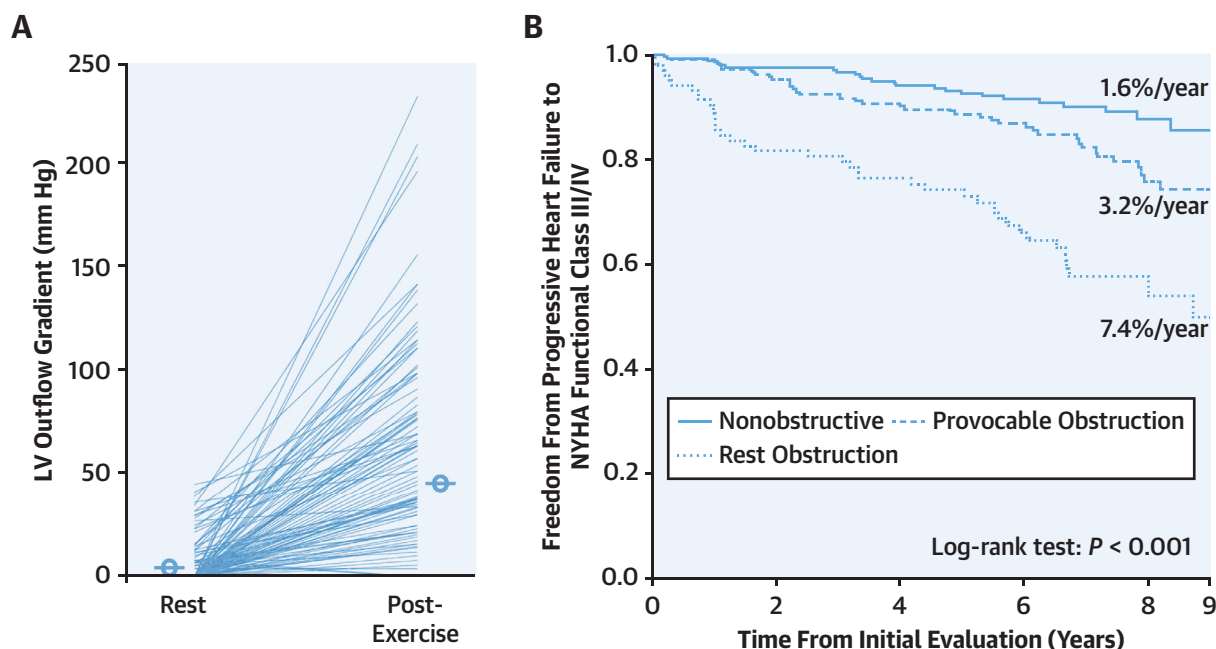


and practices with particular imaging and technical experience. CMR imaging, while synergistic with echocardiography, has certain advantages for diagnosis and risk stratification (**Figure 5**)^{3-5,32-34}; 1) when echocardiography is of suboptimal diagnostic quality; 2) provides enhanced precision of ventricular septal thickness measurement by distinguishing right ventricular muscular structures (eg, crista supraventricularis or moderate band); 3) identification of hypertrophy in areas of LV sometimes anatomically blind to echocardiography (eg, apex and anterolateral free wall), as well as subtle morphologic features in gene carriers without LVH, including narrow blood-filled myocardial crypts, elongated mitral leaflets, and expanded extracellular space³⁻⁵; 4) quantitation of LV mass and function; 5) in vivo myocardial tissue characterization with late gadolinium enhancement (LGE) representing scar

burden (fibrosis)³⁵⁻³⁸; 6) preoperative planning before invasive septal reduction to define LV outflow tract anatomy; and 7) enhances sudden death risk stratification.

Of note, in contrast to the 2020 American Heart Association (AHA)/American College of Cardiology (ACC) guidelines,⁶ the panel favors contrast CMR as a highly recommended component of a comprehensive best care model for HCM evaluation, obtained on initial evaluation and probably every 3 to 5 years depending on individual clinical assessment. CMR is relevant to the reliable morphologic diagnosis of HCM, as well as in formulating sudden death risk stratification, and contributing to suspicion of phenocopies or infiltrative storage diseases. CT imaging is useful when echocardiography is technically unreliable and CMR unavailable, or when angina is the predominant symptom.

FIGURE 4 Clinical Significance of Echocardiographic Assessment of LV Outflow Obstruction



(A) Changes to left ventricular (LV) outflow tract gradient from basal (rest) to immediately after physiologic (exercise) provocation in 200 hypertrophic cardiomyopathy patients.⁷² Each exercised patient is depicted by a line connecting the 2 gradient measurements. \emptyset = group means. Reproduced with permission from Maron et al.⁷²

(B) Relation of gradients at rest or with exercise provocation (while NYHA functional class I/II) to subsequent progressive heart failure (New York Heart Association [NYHA] functional class III/IV).

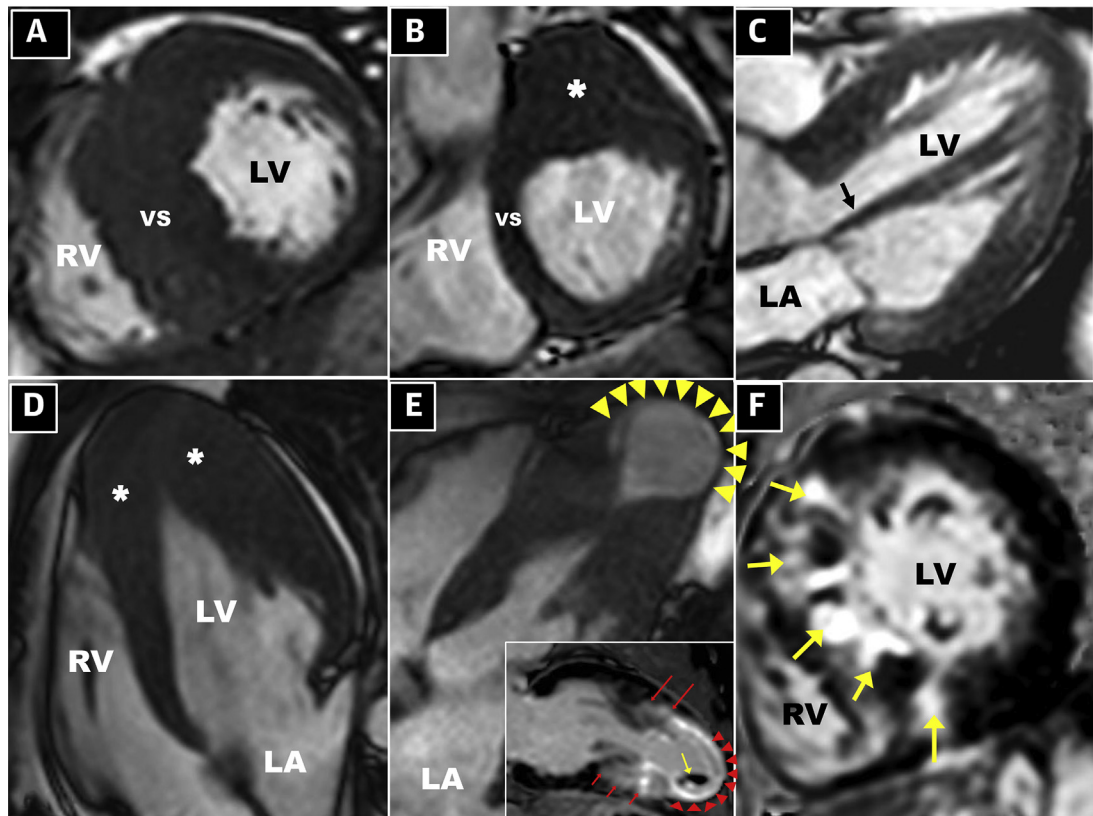
DIFFERENTIAL DIAGNOSIS. Recognition of HCM in patients with long-standing systemic hypertension is a not uncommon clinical dilemma. Differential diagnosis is most challenging when maximal LV wall thickness is in the range of 13 to 18 mm, consistent with both diseases. In such patients potentially with 2 diseases, there are no independent clinical markers capable of reliably distinguishing HCM. However, clinical clues favoring HCM include: 1) systolic anterior motion and mitral valve-septal contact with a subaortic gradient estimated by echo-Doppler; 2) maximum anterior septal thickness ≥ 18 mm; 3) patterns of LV hypertrophy predominantly involving the apex, anterolateral free wall, or posterior septum; and 4) prominent or diffuse LGE. Twelve-lead ECGs, which have no proven role in sudden death risk stratification, can identify ventricular pre-excitation and suggest phenocopies, or future development of LV hypertrophy.

HCM can be distinguished from physiologic athlete's heart by presence of cardiac symptoms, LV thickness >15 mm, (particularly if hypertrophy spares anterior septum); normal or small LV cavity

dimension, evidence of diastolic dysfunction, typical mitral valve systolic anterior motion, and dynamic LV outflow obstruction at rest or with exercise.³⁹

GUIDE TO CLINICAL MANAGEMENT.

- 1. Patients suspected of HCM should undergo diagnostic imaging with both echocardiography and contrast CMR, as well as a 12-lead ECG.**
- 2. Serial imaging should be performed with echocardiography to assess LV wall thickness; LV outflow gradient; mitral valve regurgitation; ejection fraction; left atrial diameter, volume, and function; and pulmonary arterial pressure.**
- 3. Physiologic stress (exercise) echocardiography is the preferred method for provoking labile LV outflow gradients, although sympathomimetic drug infusion, Valsalva maneuver, or amyl nitrite inhalation can be substituted in selected patients unable to exercise optimally.**
- 4. CMR is particularly useful for identifying LV apical aneurysms with regional scarring, or with contrast echocardiography (such as in patients with an ICD).**

FIGURE 5 Cardiac Magnetic Resonance in Hypertrophic Cardiomyopathy

Demonstrates the broad HCM morphologic spectrum, including high-risk phenotypes. **(A)** Massive septal hypertrophy, an independent sudden death risk marker. **(B)** Hypertrophy confined to anterolateral free wall (asterisk), an area that can be blind to the echo beam, and identifiable only with cardiac magnetic resonance. **(C)** Anomalous insertion of anterolateral papillary muscle (arrow) directly into base of anterior mitral leaflet (in absence of interpositioned chordae tendineae) that apposes the anterior septum in systole producing muscular midventricular obstruction. **(D)** Apical hypertrophic cardiomyopathy with hypertrophy confined to the distal LV chamber showing "spade-like" contour (asterisks). **(E)** Medium-sized thin-walled LV apical aneurysm (arrowheads) associated with midventricular muscular apposition of septum and free wall. (Inset) Aneurysm (red arrowheads) with adjacent areas of late gadolinium enhancement (fibrosis) (small red arrows) with susceptibility to ventricular tachyarrhythmia, and intracavitary thrombus conveying risk for embolic stroke (white arrow). **(F)** High-intensity septal late gadolinium enhancement (arrows) in a patient with preserved ejection fraction at high arrhythmic risk who subsequently experienced appropriate implantable cardioverter-defibrillator therapy. RV = right ventricle; other abbreviations as in Figure 3.

5. **CMR is useful in preoperative planning of surgical myectomy.**
6. **Follow-up serial imaging with contrast CMR about every 3 to 5 years can identify increased LGE (fibrosis), change in LV thickness, or decreasing ejection fraction.**

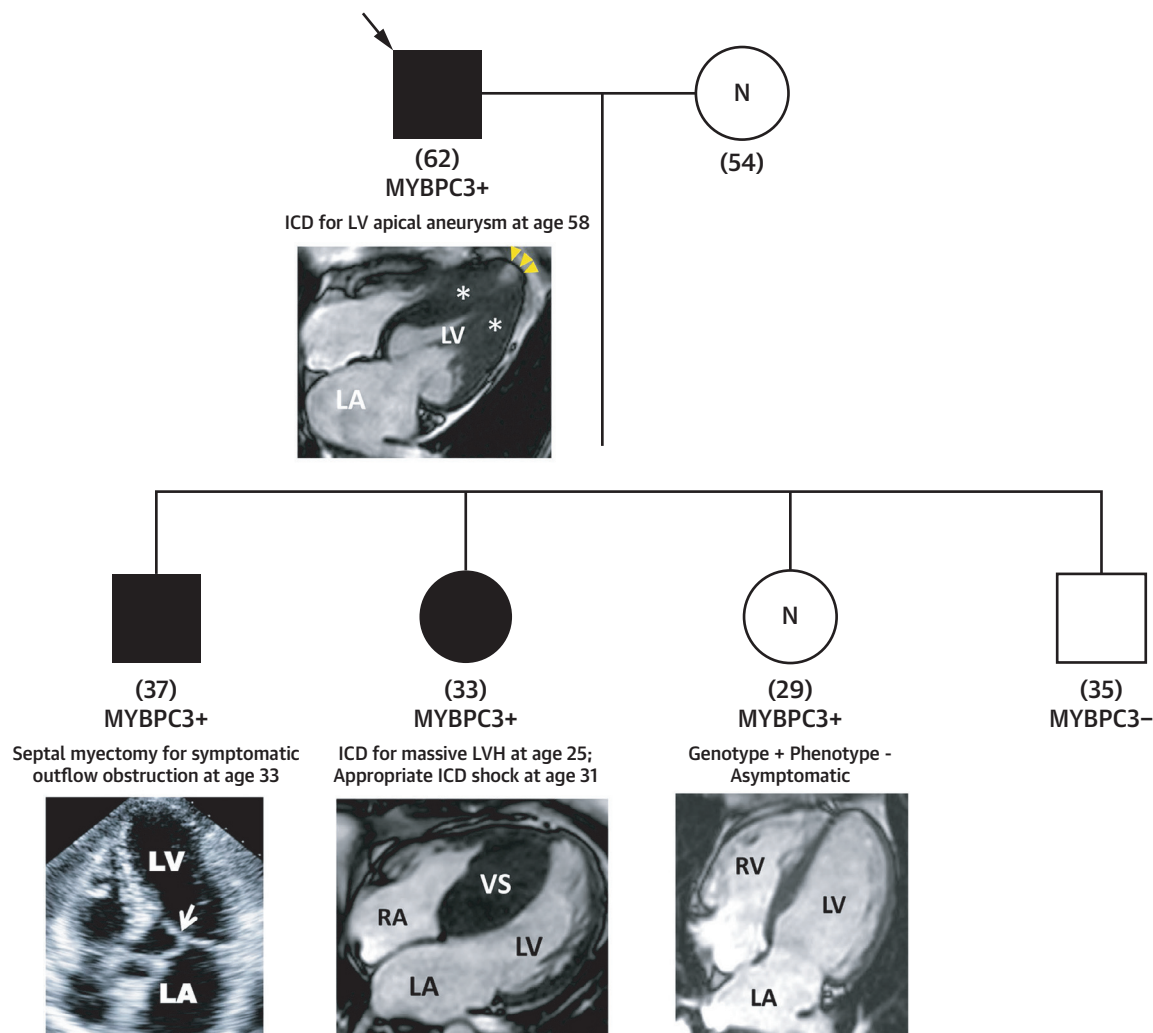
GENETIC TESTING AND ANALYSIS

Genetic testing has a role in family screening and identification of HCM phenocopies, but sarcomere mutations do not predict sudden death, prognosis, or future clinical course of individual patients.

HCM can be inherited as a Mendelian autosomal dominant disorder with variable penetrance, associated with variants in genes encoding proteins of the cardiac sarcomere involved in contractile function.⁴⁰⁻⁵⁰ The monogenic sarcomere hypothesis has been largely responsible for consolidating this heterogeneous disease into a single clinical entity.

With introduction of commercially available genetic testing, 11 or more genes have been identified in HCM patients (*MYBPC3* and *MYH7*, by far the 2 most common), but now with >2,000 individual variants, some designated as "private" (unique to individual families), or others considered likely pathogenic and

FIGURE 6 Genetic Testing Pedigree Analysis With Cascade Screening



Imaging in a hypertrophic cardiomyopathy family (positive for pathogenic *MYBPC3* gene). The proband father has LV apical aneurysm (arrows), and 3 of 4 offspring are also positive for the *MYBPC3* gene. Only 2 of the 3 offspring are phenotypically positive, while the 29-year-old daughter is genotype positive but phenotypically negative (ie, without LV hypertrophy [LVH]), demonstrating variable penetrance. ICD = implantable cardioverter-defibrillator; N = normal; RA = right atrium; RV = right ventricle; other abbreviations as in Figure 3.

disease causing,^{40-42,45-47,50} including rare pathologic variants in middle-aged adults.⁵¹

Obstacles in judging mutational pathogenicity include difficulty in reliably distinguishing rare variants from background “noise” created by sarcomeric genes evident in healthy populations.⁴⁸

Genetic testing plays an important role in family screening and in the identification of phenocopies but requires careful interpretation (Figure 6). While some investigators have reported that patients with sarcomere mutations have greater disease burden (including HF) than patients without such

mutations,⁴⁹ it is now well established that such mutations and genetic etiology do not reliably predict prognosis, future clinical course, or outcome (including sudden death risk) and therefore cannot guide management for individual patients.

Furthermore, and notably, only a minority of clinically diagnosed HCM patients (ie, 30%) have evidence of a genetic etiology with pathogenic disease-causing mutations, and therefore most patients fulfilling a clinical HCM diagnosis do not have a sarcomere mutation.⁵²⁻⁵⁵ Also, these variants fail to explain the heterogeneity of phenotypic expression and

many of the clinical or morphologic disease features in most patients.^{47,56} Despite early enthusiasm, multiple sarcomere mutations have not proven to be reliable markers for adverse prognosis.^{6-8,42} Therefore, of the many variants reported in HCM few have convincing causative roles or a gene-to-disease relationship.

Of note, variant assignments for pathogenicity (ie, most commonly as missense mutations) are considered only probabilistic. Hence, there is some degree of inherent uncertainty predicated on multiple and largely inferential criteria that differ among independent genetic testing laboratories and experts, absent widely accepted guidelines and robust cosegregation data.⁴⁰⁻⁴² At present, much of the mechanistic work related to sarcomeric proteins in HCM continues to be in laboratory experimentation with murine models, or cell culture (“diseases in a dish”), or with gene editing initiatives.^{1,56,57}

Given that sarcomere mutations track with LV hypertrophy in some HCM families, an important role for genetic testing lies with next generation (cascade) testing of at-risk and usually asymptomatic family members.^{40,41} When a proband tests positive for a pathologic sarcomere mutation, relatives who test negative for the same (or other) sarcomere variants and are considered unaffected could probably be released from lifelong imaging and clinical surveillance.

Particularly relevant to family screening with genetic testing, in 5% to 10% of families studied the initial variant assignment may represent either a false positive or false negative test result, leading to misclassification of DNA variants and genetic misdiagnosis, ultimately requiring reclassification as new information becomes available to testing laboratories and publicly accessible databases (eg, ClinVar).^{45,46,48,50}

For all these considerations, the panel finds itself in disagreement with the uniform and strict Class I recommendations found in the 2020 HCM-AHA/ACC guidelines,⁶ supporting genetic testing in virtually all patients or family members suspected of (or with) a HCM diagnosis.

Genetic testing also identifies clinically silent genetically affected family members without the HCM phenotype (ie, LV hypertrophy) (Figure 6). This preclinical subset, known as “gene positive-phenotype negative,” has the capability of disease transmission to offspring^{26,28,49} but is associated with both negligible adverse event rates and relatively infrequent phenotypic conversion during adulthood

(with some gene carriers achieving advanced ages without LV hypertrophy).

We also underscore the role of trained genetic counselors in clarifying the significance of gene carriers and others within the broad clinical HCM spectrum, as well as ever-changing interpretations of variants, ie, adjudicating results of genetic testing, including for pathogenicity, and also in organizing cosegregation pedigree studies.⁴⁶

Importantly, targeted genetic testing panels can identify nonsarcomeric cardiac, metabolic, or systemic conditions associated with LV hypertrophy that clinically mimic HCM (eg, lysosomal storage diseases such as *LAMP-2* [Danon] cardiomyopathy, *PRKAG2*, Fabry disease, Noonan syndrome and other RASopathies, and transthyretin cardiac amyloidosis).⁵⁸ Because these phenocopies differ distinctly from sarcomeric HCM with respect to natural history and treatment strategies, differential diagnosis defines a key role for genetic testing in such patients. However, such testing to distinguish HCM in patients with longstanding systemic hypertension, or physiologic hypertrophy (“athlete’s heart”), has been associated with a low mutational yield.¹⁹

Preimplantation genetic diagnosis testing is a potentially impactful strategy for avoiding transmission of phenotypic HCM when 1 parent is affected. However, pre-implantation genetic diagnosis is a highly specialized and costly procedure requiring invasive in vitro fertilization for which there is limited experience in HCM.

GUIDE TO CLINICAL MANAGEMENT.

- 1. All HCM patients and families should have systematic genetic counseling relevant to the disease, including before planned conception.**
- 2. Genetic testing should not be performed in families unless a pathogenic (or likely pathogenic) variant has been identified in the proband. Family genotyping is not indicated when proband has no mutation or variant of unknown significance.**
- 3. In accord with wishes of proband or family, genetic testing can be performed to identify inheritance in next generation offspring (or other relatives) without LV hypertrophy.**
- 4. Genetic testing can be particularly informative in differential diagnosis of HCM phenocopies (eg, *LAMP-2* [Danon], Fabry disease, other storage diseases, and cardiac amyloidosis), but has low yield in the differential diagnosis of HCM versus physiologic athlete’s heart and systemic hypertension.**

5. **Families undergoing genetic testing should be informed that the possibility of future variant reassignment could alter the initially considered inheritance pattern.**
6. **Patients should be advised that mutational analyses can potentially create genetic discrimination for life, disability, and long-term care insurance. However, the 2008 Genetic Information Act prohibits discrimination in employment and health insurance based on genotype.**
7. **Currently, there is no evidence supporting routine genetic testing to assess prognosis or risk stratification, given that single or multiple sarcomere mutations do not predict future clinical course of HCM.**

HCM SCREENING IN FAMILIES

Diagnostic imaging, the preferred strategy for screening family members for HCM phenotypes usually begins at 12 years, extending to 18 to 21 years of age. Thereafter, imaging can be repeated at about 5-year intervals, in the absence of resolution by genetic testing.

Screening for HCM in first-degree and other close family relatives is a recommended strategy (Figure 6).^{6-8,24} The preferred initial approach relies on noninvasive imaging with echocardiogram and CMR (and ECG) to identify otherwise unexplained LVH as the disease marker (phenotype).^{4,5} Distinctly abnormal 12-lead ECG patterns (ST-T abnormalities, increased voltages, deep Q waves, or pre-excitation) can raise suspicion of HCM in family members, sometimes even before LVH is evident by imaging.

Because evidence of the HCM phenotype and adverse events uncommonly occur before adolescence, it has been a standard recommendation not to initiate routine echocardiographic screening in young relatives until about 12 years of age, but potentially earlier when associated with: accelerated growth; premature puberty; or particular clinical circumstances (eg, malignant family history, suggestion of LV outflow tract obstruction, symptom onset); or when systematic training is contemplated in vigorous sports programs for young children.^{6,7,24,59} Conversion to the HCM phenotype can often be predicted by 12-lead ECG abnormalities.^{44,60}

There has been some recent interest in pediatric cardiology for identifying HCM with screening at very early ages (<10-12 years), including in infants.^{6,27,61} However, there are several major counterbalancing

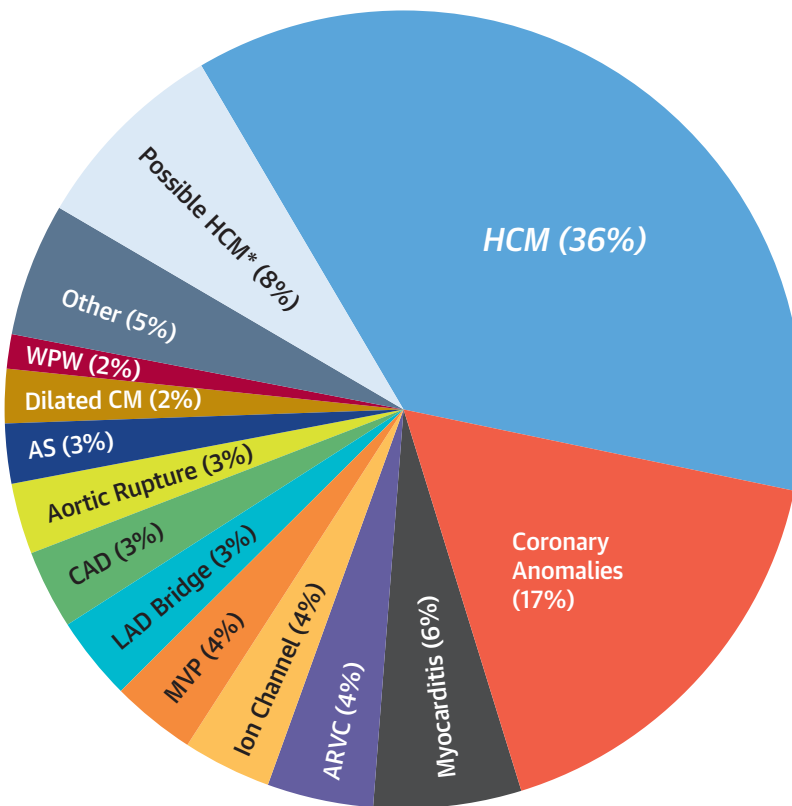
issues to such a strategy, including the infrequency with which LV hypertrophy is identifiable in this age group.⁵⁹ Also, while sudden death events could theoretically be prevented by early screening, such events are exceedingly uncommon <12 years of age,¹⁹ and would promote prophylactic defibrillators in very young patients. Furthermore, routine echocardiographic screening of preadolescents could create diagnostic uncertainty related to interpretation of LV wall thicknesses relative to body size during periods of rapid growth. Imprecision in identifying the HCM phenotype (ie, LVH) increases the risk for false positive diagnosis or potentially unnecessary recommendations such as withdrawal from sports. Given the rarity of HCM events^{6,7,24} and the limited justification for major prophylactic therapeutic interventions in the first decade of life (such as ICDs), routine screening of very young children could create needless anxiety (and cost) for otherwise healthy patients.

The HCM phenotype can demonstrate variable penetrance with a delay in appearance well past adolescence into young adulthood and even middle age (Figure 6).^{6,7,24,43,44,61,62} This recognition can justify extending diagnostic imaging to adult family members, at 5-year intervals, particularly when 12-lead ECG abnormalities are evident, and genetic testing is not informative.^{44,60} A common apparently nonfamilial (non-Mendelian) sporadic form of HCM without sarcomere mutations can be encountered in clinical practice.⁶³

Therefore, because the evidence does not support very early screening, the panel favors the prudent and more practical recommendations in the 2011 ACC/AHA guidelines,⁷ the 2003 ACC/European Society of Cardiology consensus,²⁴ and the relevant literature,⁵⁹ largely limiting routine echocardiographic screening studies to asymptomatic family members of at least 12 years of age.

GUIDE TO CLINICAL MANAGEMENT.

1. **Clinical HCM family screening is recommended for first-degree and other close relatives, performed initially by contemporary imaging (echocardiography and CMR), to assess inheritance of HCM phenotypes (ie, LVH).**
2. **Genetic testing is not considered the preferred initial strategy for diagnostic screening of family members, given its low yield of disease-causing mutations and frequent uncertainty regarding pathogenicity.**

FIGURE 7 Causes of Sudden Death in Competitive Athletes

A variety of congenital, genetic or acquired abnormalities are responsible for these events, with hypertrophic cardiomyopathy (HCM) the single most common accounting for about one-third, (based on U.S. registry data).⁶⁴⁻⁶⁶ *Modest but unexplained LV hypertrophy. ARVC = arrhythmogenic right ventricular cardiomyopathy; AS = aortic stenosis; CAD = coronary artery disease; CM = cardiomyopathy; LAD = left anterior descending artery; MVP = mitral valve prolapse; WPW = Wolff-Parkinson-White syndrome.

3. In accord with the wishes of proband or family, cascade genetic testing can be performed in next generation offspring (or other relatives) without LVH to identify sarcomere gene carriers.
4. Other than in exceptional circumstances, screening of family members begins at about 12 years, continuing at 12- to 36-month intervals until 18-21 years when full growth and maturation is achieved; screening can be reasonably extended every 5 years into adulthood with imaging at physician discretion, particularly if the 12-lead ECG is abnormal.

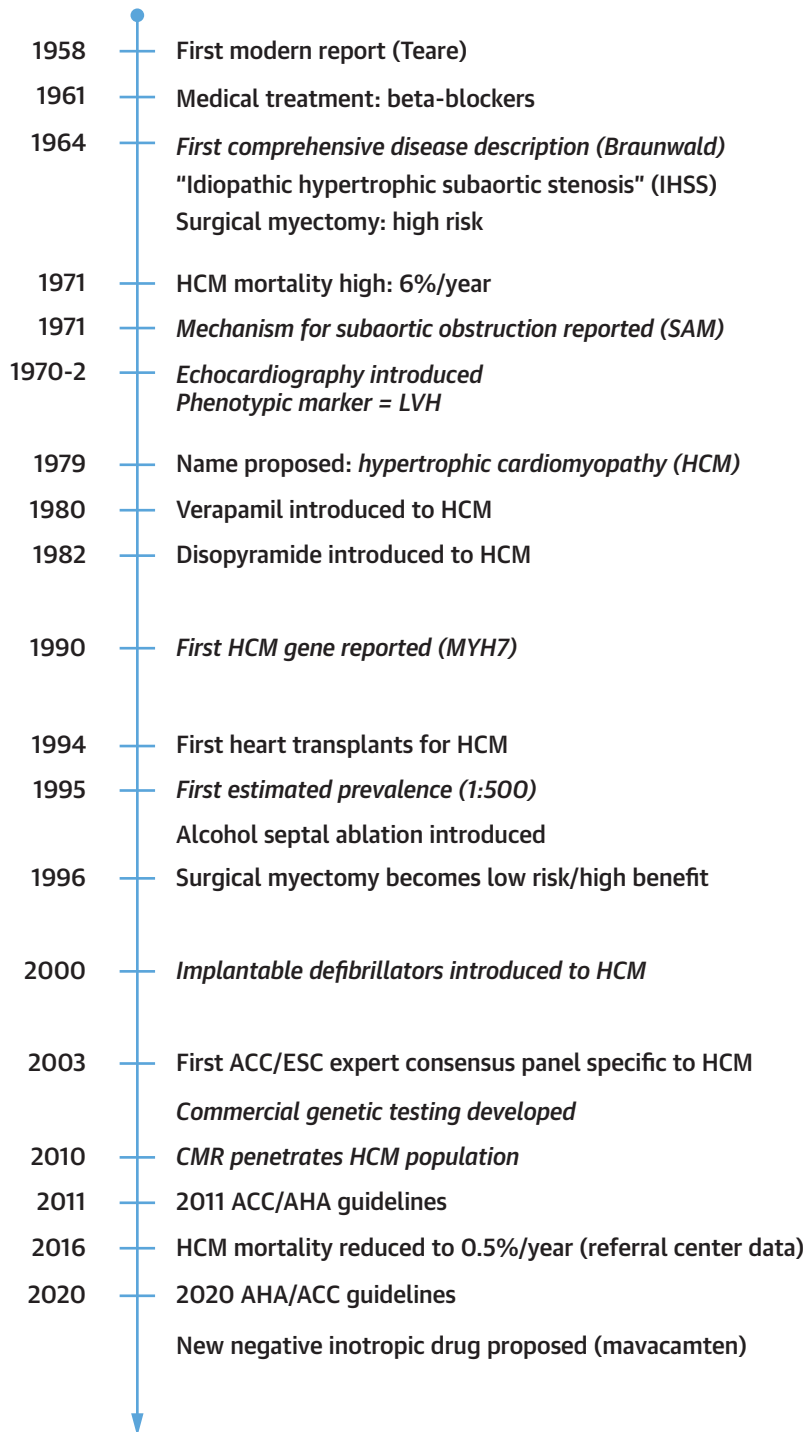
EXERCISE, PHYSICAL ACTIVITY, AND ATHLETES

HCM is an important cause of sudden death in young competitive athletes, as intense sports participation can increase arrhythmic risk, supporting consideration for prudent disqualification to prevent catastrophic events on the athletic field.

DEMOGRAPHICS AND SUDDEN DEATH. HCM is frequently responsible for non-trauma-related sudden deaths in young asymptomatic student-athletes, accounting for about one-third of these catastrophic events (in U.S. registry data), predominantly in basketball and football (Figure 7).⁶⁴⁻⁶⁶ A variety of other predominantly congenital or genetic heart diseases are responsible for the remainder, including coronary anomalies with wrong sinus origin, myocarditis, and arrhythmogenic right ventricular cardiomyopathy (common in reports from Italy).⁶⁶ A minority of such events are associated with normally structured hearts, some of which may represent undiagnosed ion channelopathies.^{67,68} It should also be recognized that many sudden deaths in HCM patients (about 60%) occur under sedentary conditions or with only mild or routine physical activity, and not exclusively in athletes.⁶⁸⁻⁷⁰

There are compelling data and consensus documents that incriminate participation in

FIGURE 8 Timeline of Key Advances in HCM



ACC = American College of Cardiology; AHA = American Heart Association; ESC = European Society of Cardiology; HCM = hypertrophic cardiomyopathy; SAM = systolic anterior motion.

intense competitive sports as a trigger for cardiac arrest in susceptible individuals with HCM, particularly those with ≥ 1 major sudden death risk markers, LV outflow obstruction, or prior symptoms such as unexplained syncope.^{1,6-8,19,24,65,71,72} Over 25 years, 5 previous U.S. and European consensus panels have considered HCM as a modifiable risk marker supporting consideration for disqualification of young athletes with HCM from organized intense competitive sports potentially as a life-saving measure to prevent sudden arrhythmic death and assure the safety of the athletic field.^{71,73}

ELIGIBILITY VS DISQUALIFICATION. Indeed, because the level of risk incurred by patients with HCM engaged in an intense competitive sports lifestyle is exceedingly difficult to stratify with precision for each individual athlete, eligibility/disqualification decisions can prove complex and unavoidably (and unfortunately) result in exclusion of some low-risk individuals from the attributes of competitive sports.

The panel is aware of an emerging interest in liberalizing eligibility for competitive student-athletes with HCM and other cardiovascular diseases by providing greater autonomy to the athletes for participation in organized high school and college sports. However, the panel does not regard this strategy as enhancing the safety of the athletic field.⁶

Therefore, after weighing the available evidence, we depart from the 2020 AHA/ACC recommendation⁶ that makes eligibility for competitive sports largely a matter of athlete preference within the shared decision model, ie, the individual athlete-patient becomes responsible for their own fate should they choose to play competitive sports with cardiovascular disease and cautious physician-mediated recommendations are regarded as paternalistic.

Therefore, the panel continues to support the prudent recommendation for disqualifying most athletes with HCM from intense competitive sports in order to reduce sudden death risk in the athletic arena.^{7,65} It is also possible that some disqualified athletes with HCM will be judged at high sudden death risk with risk markers sufficient to become candidates for primary prevention ICDs thereafter.¹⁸

Responsibility for eligibility and disqualification decisions in student athletes with cardiovascular diseases (such as HCM) should rest primarily with those physicians who best understand the risks to their individual patient, and specifically team physicians for high school and college sports. Abdicating responsibility for medical decisions transforms the clinician's role from an active one to that of a passive

participant empowering autonomous patient decisions that could ultimately expose young people to unnecessary risks.⁷⁴

This perspective is supported by the precedent-setting *Knapp v. Northwestern* decision⁷⁵ which is established law that asserts eligibility and disqualification decisions for student athletes with medical disabilities (such as HCM) should remain the inherent and primary responsibility of the "third-estate" ie, the team physician relying on consultants and consensus guidelines as representative of the educational institution empowered to protect the health and safety of student-athletes.

The 2020 AHA/ACC guidelines for HCM⁶ oppose the prudent and established legal principle of *Knapp v. Northwestern*, but without new evidence to support reversing the precedent previously expressed in the 2011 ACC/AHA guidelines.⁷ Although controversial, some clinicians favor participation in intense competitive sports for high-risk patients with implanted defibrillators (including those with HCM), despite high appropriate and inappropriate shock rates.⁷⁶

Finally, at present, there is no compelling evidence that participation in regular recreational and noncompetitive aerobic-type physical exercise of moderate intensity itself elevates arrhythmic risk or promotes disease progression in HCM.^{77,78} Prudent and useful cardiovascular fitness programs tailored to HCM can be found online.⁷⁹

GUIDE TO CLINICAL MANAGEMENT.

- 1. In accord with prior ACC-sponsored Bethesda Conferences and AHA/ACC consensus guidelines, HCM is usually considered a disqualifying condition from most sanctioned high school and intercollegiate competitive sports for the purpose of reducing sudden death risk on the athletic field.**
- 2. HCM patients are discouraged from sports activities involving accelerated running (sprinting) associated with abrupt increase in heart rate or development/increase in LV outflow obstruction, or isometric weight training.**
- 3. Athletic situations that are restrictive and in which it is difficult for participants to terminate independently (should potential cardiovascular symptoms arise) are not recommended.**
- 4. Primary prevention ICD implants as a strategy to permit participation of at-risk HCM patients in competitive sports is not recommended, given the high shock rates reported.**
- 5. Moderate noncompetitive aerobic exercise programs to improve cardiorespiratory fitness, as part of developing healthy lifestyles, are acceptable.**

CONCLUSIONS AND PERSPECTIVES

During the last 50 years, multidisciplinary imaging in HCM has evolved and achieved a high level of diagnostic sophistication (Figure 8). Synergistic with echocardiography, CMR has over the last decade been an important part of that progress, and merits full utilization in the HCM clinical environment, ie, including during the initial comprehensive patient evaluation, as well as subsequently about every 3 to 5 years, as judged by the individual clinical circumstances. The strength of CMR lies with its high resolution and tomographic imaging capability which promotes reliable HCM diagnosis, as well as risk stratification via extensive LGE.

Identification of the HCM phenotype during cascade family screening relies initially on echocardiography or CMR imaging but can be supplemented with genetic testing to more conclusively determine the affected status of preclinical phenotype-negative relatives. However, routine diagnostic echocardiographic imaging in very young (<10-12 years of age) family members can be fraught with uncertainty or false positive diagnoses that create anxiety and may lead to unnecessary clinical recommendations, even though therapeutic interventions are seldom indicated for asymptomatic patients during the first decade.

The genetics of HCM is complicated by heterogeneity, incomplete penetrance, variable expression and phenocopies, as well as the difficulty in reliably establishing pathogenicity with testing. Furthermore, increasingly, it is evident that the 30-year single-gene (monogenic) causation hypothesis for HCM lacks robust evidence in many respects, for example, a firm genetic etiology can be identified in only a minority (ie, 30%) of clinically diagnosed patients. Alternatively, it is possible that the genesis of HCM may be multifactorial and involve nongenetic or environmental factors.

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