Hypertrophic cardiomyopathy (HCM) is a clinically heterogeneous disease, ranging from asymptomatic incidental diagnoses to the most serious outcomes of heart failure and sudden cardiac death (SCD). HCM occurs in at least 1 in 500 of the general population, making it one of the commonest inherited heart diseases. Research efforts over the last 2 decades have focused on identifying predictors of poor outcomes among HCM patients, including development of atrial fibrillation, heart failure, need for cardiac transplantation, and nonasymmetric septal morphology. These efforts have been complicated by the vast clinical diversity seen among probands and within families.

Background—Yield of causative variants in hypertrophic cardiomyopathy (HCM) is increased in some probands, suggesting different clinical subgroups of disease occur. We hypothesized that a negative family history and no sarcomere mutations represent a nonfamilial subgroup of HCM. We sought to determine the prevalence, natural history, and potential clinical implications of this nonfamilial subgroup of HCM.

Methods and Results—Four hundred and thirteen unrelated probands with HCM seen in a specialized HCM center between 2002 and 2015 and genetic testing performed were included in this retrospective cohort study. There were 251 (61%) probands with no reported family history of HCM, including 166 (40% of total) probands with no sarcomere mutation, that is, nonfamilial HCM. Quantified family pedigree data revealed no difference in mean number of first-degree relatives screened between nonfamilial and sarcomere-positive groups. Adjusted predictors of nonfamilial status were older age (odds ratio, 1.04; 95% confidence interval, 1.02–1.06; \( P = 0.0001 \)), male sex (odds ratio, 1.96; 95% confidence interval, 1.11–3.45; \( P = 0.02 \)), hypertension (odds ratio, 2.80; 95% confidence interval, 1.57–5.00; \( P = 0.0005 \)), and nonasymmetric septal morphology (odds ratio, 3.41; 95% confidence interval, 1.64–7.08; \( P = 0.001 \)). They had a less severe clinical course with greater event-free survival from major cardiac events (\( P = 0.04 \)) compared with sarcomere-positive HCM probands. Genotype prediction scores showed good performance in identifying genotype-positive patients (area under the curve, 0.71–0.75) and, in combination with pedigree characteristics, were further improved.

Conclusions—Approximately 40% of HCM probands have a nonfamilial subtype, with later onset and less severe clinical course. We propose a revised clinical pathway for management, highlighting the role of genetic testing, a detailed pedigree, and refined clinical surveillance recommendations for family members. (Circ Cardiovasc Genet. 2017;10:e001620. DOI: 10.1161/CIRCGENETICS.116.001620.)

Key Words: family history, genetic testing, genetics, human, hypertrophic cardiomyopathy, sarcomere

See Clinical Perspective

HCM is an autosomal dominant disease caused by mutations in sarcomere or sarcomere-related genes. First-degree relatives are advised to have periodic clinical surveillance with a cardiologist, given their 50% risk of disease. The ongoing need for clinical surveillance of family members produces a significant resource burden for the health system and provides uncertainty for the relatives regarding their risk of future clinical events. The collection of a detailed 3-generation family history, while time consuming and best performed by those with expertise, can contribute to more accurate diagnosis,
understanding of family dynamics, and familial inheritance risks. Genetic testing is recommended for all probands, and if a disease-causing variant is identified, family members may undergo cascade genetic testing.

Clinical diagnostic criteria specify HCM as unexplained left ventricular (LV) hypertrophy of ≥15 mm, associated with nondilated ventricular chambers in the absence of another cardiac or systemic disease that itself would be capable of producing the magnitude of hypertrophy evident in a given patient. However, there is growing recognition that clinically distinct subgroups of HCM patients exist. Those with more severe disease, younger age at onset, and positive family history will have a greater pretest probability of a positive gene result, with a yield of ≤70%. Genotype prediction scores based on these clinical characteristics, such as the Toronto and Mayo scores, have shown good predictive capacity. The remaining patients, who are typically older, with no family history and inevitably no causative variant identified, are not well characterized and at present managed the same as familial HCM cases. We hypothesize that the broad definition of HCM likely encompasses a heterogeneous mix of underlying pathogeneses, including an important subgroup with no family history of disease and no sarcomere gene variant, that is, nonfamilial HCM. We sought to define whether nonfamilial HCM exists, determine the prevalence and most effective methods for identifying this group, evaluate the natural history compared with sarcomere-positive HCM, and use this to refine clinical recommendations relating to family surveillance.

### Methods

#### Consecutive Patient Series and Clinical Data Collection

This was a retrospective cohort study. Consecutive unrelated patients seen in a tertiary referral center between February 2002 and December 2015, with a definite clinical diagnosis of HCM and genetic testing performed, were included. Clinical diagnosis was made according to disease guidelines, including LV wall thickness of ≥15 mm, with the diagnosis confirmed in a specialized HCM center. Clinical data were collected from the medical record, or the Australian Genetic Heart Disease Registry. Human research ethics committee approval was obtained, and participants gave written informed consent. Echocardiographic and electrocardiographic measurements were included as previously described. LV outflow tract obstruction was defined as a gradient of ≥30 mm Hg at rest or ≥50 mm Hg with exercise. Septal morphology was defined as asymmetric (ie, reverse curvature) or nonsymmetric (eg, apical, concentric). Nonsustained ventricular tachycardia was defined as ≥3 consecutive beats of ventricular tachycardia at a rate of ≥120 bpm. SCD events were defined as SCD, resuscitated cardiac arrest, or implantable cardioverter defibrillator (ICD) shocks after ventricular fibrillation.

#### Study Groups

Nonfamilial HCM patients were defined as those with no overt family history of HCM (ie, 1 affected proband) and genetic testing of at least 7 HCM genes performed with no causative variants identified. Sarcomere-positive patients were those with a causative sarcomere gene variant, regardless of family history status (Figure 1).

#### Family Pedigree Analyses

A 3-generation family history was collected by a cardiac genetic counselor as per clinical practice, and a positive family history was defined as ≥1 relatives with a confirmed clinical diagnosis of HCM (ie, a total of ≥2 affected in a family, at any age; confirmed by cardiac investigations, correspondence with the clinician, or death certificate/postmortem report as per clinical practice). A family history of SCD included any death occurring at any age in a sudden manner with either a pre-morbid diagnosis of HCM or HCM confirmed on postmortem examination. Quantitative data were derived from the pedigree and included: total family size (proband and all first-degree relatives ≥18 years), total living family size (proband and living first-degree relatives ≥18 years), number of parents alive (0, 1, and 2), number of siblings ≥18 years and alive, number of children ≥18 years and alive, and total number of first-degree relatives ≥18 years with clinical screening.

#### Genetic Analyses and Variant Classification

Outcomes of genetic testing (performed either commercially or on a research basis) were recorded. Rare variants with a minor allele frequency of ≤0.02% in the Exome Aggregation Consortium data set (http://exac.broadinstitute.org/) in established HCM genes (MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL2, MYL3, ACTC1) were considered. Probands with causative variants in HCM phenocopies (PRKAG2, LAMP2, GLA) and atypical HCM phenotypes (ACTN2, PLN) were excluded from further analysis. Clinical classifications were used where possible, using in-house criteria (see ClinVar, Agnes Ginges Center for Molecular Cardiology variant assessment and assertion criteria: https://submit.ncbi.nlm.nih.gov/ft/clinical/234/2010/09/24/3636-505375.Agnes-ginges_variantseval clinvar.pdf), and those classed as likely pathogenic or pathogenic were considered causative. Given the conservative approach to clinical classifications and recent data to suggest these are likely too stringent, variants of uncertain significance (VUS) were further assessed using research classifications and considered causative if they fulfilled all 3 criteria: (1) very rare, seen in Exome Aggregation Consortium <0.02%, (2) in an established HCM gene, and (3) 3 out of 4 in silico tools supportive of a deleterious effect (GERP>2, Polyphen-2 [http://genetics.bwh.harvard.edu/pph2/] = “Pathogenic”, Polyphen-2 [http://genetics.bwh.harvard.edu/pph2/] = “Probably damaging”, SIFT [http://sift-dna.org/] = “Deleterious”). Those not meeting these criteria remained as VUS, and these probands were excluded from subsequent analyses. Variants classified as causative using research criteria are shown in the Data Supplement, and these classifications should not be used in a clinical setting. All variants and classification are shown in the Data Supplement.

#### Stringent Nonfamilial HCM Group

A more stringent subgroup of nonfamilial HCM probands was created to identify only those probands where extensive family investigations had been performed to increase the certainty of a true negative family history. Only probands where ≥2 adult first-degree relatives had undergone clinical screening with a cardiologist were included. Confirmation of clinical surveillance of relatives was performed to ensure that the family information was correct, which included assessment within our own center, correspondence from the clinician, or reviewing echocardiogram reports. In addition, this group had a minimum of 11 genes screened (established HCM genes and phenocopies).

#### A Clinical Score to Identify Nonfamilial HCM

Although a family history and genetic testing will identify nonfamilial HCM disease status in many cases, a score to raise clinical suspicion of nonfamilial HCM will be of value, particularly, where family history may be inadequately known and genetic findings are unclear. Two genotype risk scores already exist15,28; however, they were developed for use in all HCM probands, regardless of their family history. Receiver operating characteristics curves were used to show an area under the curve as a marker for performance of the different clinical scores (using the predicted probabilities as a continuous variable). Clinical prediction of nonfamilial HCM was based on a logistic regression model using the Toronto genotype score (binary variable using a cutoff of ≤0.25 predicted probability to indicate low risk of a positive genotype), and further analysis was performed to identify...
clinical or family history factors that might improve detection. The number of adult children a proband has was made into a binary variable where ≥2 children indicates low risk of positive genotype.

**Statistical Analysis**

Statistical analysis was performed using Prism version 6.0 (GraphPad Software Inc., La Jolla, CA) and SAS Studio (SAS Institute Inc., Cary, NC). Chi-square analyses and unpaired t tests were used to analyze categorical and continuous variables, respectively. Clinical risk scores (Toronto and Mayo genotype prediction scores and European Society of Cardiology HCM-Risk SCD algorithm) \( 6,18,26 \) were calculated. Univariate and multivariate logistic regression analyses were performed to determine independent factors associated with nonfamilial HCM (using the stringent nonfamilial group). This was performed using a backward stepwise approach, including variables with \( P < 0.1 \) on univariate analysis and not clinically similar to another included variable (ie, age and age at diagnosis), then removing nonsignificant variables. A Kaplan–Meier plot with log-rank tests for significance was used to assess event-free survival (from cardiac death, cardiac transplant, resuscitated cardiac arrest, or ICD shock because of ventricular fibrillation) between nonfamilial and sarcomere-positive probands. The time variable was age (years) at first event or age at most recent follow-up where they were known to be free from events, ≤80 years.

**Results**

**Patient Characteristics**

The study cohort is summarized in Figure 1. There were 730 HCM probands seen from 2002 to 2015. Of these, 317 probands were excluded from further analysis because of genetic testing not being performed (eg, no DNA available, patient declined testing), family history not reliably recorded (eg, proband adopted, family living overseas), or confirmed phenocopies. Among the 413 probands included, 251 (61%) had no overt family history of disease, including 166 (40% of total) with no identifiable genetic cause, and were assigned to the nonfamilial HCM group. The sarcomere-positive group comprised 74 probands with no family history of disease, despite a positive genetic test result, as well as 116 with a positive family history and positive gene result (total n=190). Proband with a positive family history of HCM and a negative gene result (n=36) were excluded from further analysis because these likely represent new, as yet undiscovered, familial HCM or rare HCM phenocopies. There were 21 probands with unresolved VUS who were excluded.

Patients were followed for a mean of 7.2±5.0 years (range, 0–24 years), and 90% of patients had their most recent contact with the clinic within the last 5 years. Mean age of the patients was 54.5±16.5 years, 226 (64%) were male, and mean maximum LV wall thickness was 20.1±5.4 mm. All probands met clinical diagnostic criteria for HCM.

**Genetic Analysis and Variant Classification**

There were 324 probands who underwent research-based genetic testing, including 35 with a 7-gene panel, 250 with a 46-gene panel (Illumina TruSight Cardiomyopathy Sequencing Panel; Data Supplement; average coverage 325±133 reads, with 99.2%±1.6% of target regions covered at least 20x), and 38 who underwent whole exome sequencing \( 27,28 \) (analysis limited to 46-gene list; average coverage 86±11.5 reads, with 90.5%±3.4% of target regions covered at least 20x), while 90 patients had commercially available clinical genetic testing (minimum 11 genes screened). Variants identified are shown in the Data Supplement. The overall yield of causative variants was 190/413 (46%), with 103 (54%) in MYBPC3, 60 (32%) in MYH7, 12 (6%) in TNNT2, 9 (5%) in TNNI3, 4 (2%) in TPM1, and 2 (1%) in MYL3. There were 167 probands with variants, with clinical classifications of likely pathogenic or pathogenic. Of the remaining 44 VUS, research classifications were applied, and 23 VUS were upgraded to pathogenic (including 10 [5%] with no family history and 13 [7%] with a positive family history of HCM, \( P=0.635 \)). The remaining 21 VUS were excluded from further analysis (Figure 1).

Family history of HCM was significantly associated with the identification of a sarcomere mutation (71% versus 30%; \( P<0.0001 \); Figure 2A). The proportion of genes...
harboring the causative variant did not differ by family history (\(P=0.87\); Figure 2B), suggesting that there are not less penetrant genes.

**Characterization of Nonfamilial HCM Patients**

There were 190 probands assigned to the sarcomere-positive and 166 to the nonfamilial HCM groups, and key differences in clinical characteristics are shown in Table 1. Nonfamilial HCM probands accounted for 40% of the cohort and, compared with sarcomere-positive HCM, were more likely male (\(P=0.001\)), of older age (\(P<0.0001\)), of older age at diagnosis (\(P<0.0001\)), of older age at atrial fibrillation onset (\(P=0.002\)), and had greater body mass index (\(P=0.001\)). Nonfamilial HCM probands were also less likely to have nonsustained ventricular tachycardia (\(P=0.02\)), have a lower risk of SCD measured by the HCM-Risk score (\(P=0.007\), less likely to have an ICD (\(P=0.003\)), and more likely to have hypertensive (\(P<0.0001\)). Echocardiographic characteristics showed that nonfamilial HCM probands had lower maximum LV wall thickness (\(P<0.0001\)), greater posterior wall thickness (0.002), were more likely to have apical or concentric septal morphology (\(P=0.001\)), were more likely to have LV outflow tract obstruction (\(P=0.007\)), and had greater LV end-diastolic diameter (\(P=0.02\)). Because of the high likelihood of age confounding these data, they should be interpreted with caution.

**Nonfamilial HCM Probands Who Meet Stringent Family Screening Criteria**

There were 114 (69%) among the 166 nonfamilial HCM group who met stringent family screening criteria (ie, \(\geq 2\) first-degree relatives confirmed to have undergone clinical surveillance aged \(\geq 18\) years and no other family history of HCM) and comprehensive genetic testing of at least 11 genes. Compared with sarcomere-positive HCM probands, the stringent nonfamilial HCM group was clinically different in several ways on univariate analyses (Table 2). Multivariable logistic regression analysis identified older age (adjusted odds ratio [OR], 1.96; 95% CI, 1.11–3.45; \(P=0.021\)), nonsymmetric septal morphology (adjusted OR, 3.41; 95% CI, 1.64–7.08; \(P=0.001\)), and presence of hypertension (adjusted OR, 2.80; 95% CI, 1.57–5.00; \(P=0.0005\)) to be significantly and independently associated with nonfamilial HCM (Table 2; the 4 components of the Sydney Genotype Score). Sensitivity analyses to determine whether bias was introduced by exclusion of the VUS group (n=21) and gene-negative/family history–positive group (n=36) showed no changes to the overall final model.

**Using Family History Characteristics to Identify Sarcomere-Positive HCM**

Overall, the mean family size (proband plus first-degree relatives \(\geq 18\) years) was 7.6±2.5 (range, 3–16), with 2.7±1.9 (range, 0–8) first-degree relatives \(\geq 18\) years clinically screened. Comparisons between nonfamilial HCM and sarcomere-positive families identified no significant differences after adjusting for age of proband as a confounder (Table 3). Among those with no family history of HCM, sarcomere-positive probands were significantly less likely to have adult children (adjusted OR, 1.38; 95% CI, 1.04–1.82; \(P=0.02\)) compared with sarcomere-negative probands even after adjusting for age. For those with no family history, the yield of a positive gene result for those with 2 or more adult children was 26/103 (20%) compared with 46/100 (46%) for probands with one or no adult children.

The yield of genetic testing did not change significantly in those with no family history of disease as the number of first-degree relatives clinically screened increased. For those with no first-degree relatives \(\geq 18\) years clinically screened, the yield was 12/33 (36%), 1 to 3 relatives screened was 39/127 (31%), and \(\geq 4\) relatives screened was 21/89 (30%; \(P=0.805\)).

**Benign Clinical Course of Nonfamilial HCM Compared With Sarcomere-Positive Probands**

The clinical profile of nonfamilial HCM probands is summarized in Figure 3. Nonfamilial HCM probands have a less...
severe clinical course compared with sarcomere-positive HCM. Compared with sarcomere-positive HCM probands, nonfamilial HCM probands are diagnosed later in life (50±16 versus 37±17 years; \( P < 0.0001 \); Figure 3A), receive an ICD less often (25% versus 55%; \( P < 0.0001 \)), and later in life (52±13 versus 42±15 years; \( P = 0.005 \); Figure 3B), most likely because of the lesser degree of LV hypertrophy and the absence of a family history of SCD among nonfamilial HCM. The indications for ICD therapy are shown in Figure 3C. While non-sustained ventricular tachycardia was overall more prevalent among sarcomere-positive HCM (32% versus 21%; \( P = 0.02 \), it was the most frequent indication for ICD among nonfamilial HCM, accounting for 65% of all ICDs in this group. Overall, European Society of Cardiology HCM-Risk scores were significantly higher among sarcomere-positive HCM probands (4.3±3.7% versus 3.1±2.9% 5-year risk SCD; \( P = 0.007 \)).

Sarcomere-positive HCM probands (23 events; 10 SCD, 5 transplant; 6 aborted cardiac arrest, 1 ventricular fibrillation ICD shock, 1 heart failure death; mean±SE event-free survival to age 61.5±1.0 years) had worse event-free survival from

### Table 1. Characteristics of Nonfamilial HCM Versus Sarcomere-Positive HCM Probands

| Variable                        | Total       | Nonfamilial HCM | Sarcomere Positive | \( P \) Value |
|---------------------------------|-------------|-----------------|--------------------|--------------|
| N                               | 356 (100)   | 166 (46.6)      | 190 (53.4)         | …            |
| Male sex                        | 226 (63.5)  | 120 (72.3)      | 106 (55.8)         | 0.001        |
| Age                             | 54.5±16.5   | 61.2±14.9       | 49.5±16.5          | <0.0001      |
| Age at diagnosis                | 42.1±17.4   | 50.0±15.7       | 36.7±17.0          | <0.0001      |
| Follow-up time, y (range)       | 7.2±5.0     | 6.7±4.8 (0–18)  | 7.6±5.3 (0–24)     | 0.10         |
| Atrial fibrillation (AF)        | 111 (32.5)  | 58 (37.2)       | 53 (28.5)          | 0.09         |
| AF age at onset                 | 53.4±15.6   | 59.7±13.6       | 49.5±16.4          | 0.002        |
| Nonsustained VT                 | 90 (26.5)   | 33 (20.6)       | 57 (31.7)          | 0.02         |
| Unexplained syncope             | 67 (20.8)   | 31 (21.7)       | 36 (20.1)          | 0.73         |
| Heart failure                   | 22 (6.5)    | 9 (5.8)         | 13 (7.1)           | 0.61         |
| Cardiac transplant              | 8 (2.3)     | 2 (1.2)         | 6 (3.3)            | 0.21         |
| SCD event                       | 42 (11.8)   | 14 (8.4)        | 28 (14.8)          | 0.06         |
| Mean HCM-Risk score             | 3.8±3.3     | 3.1±2.9         | 4.3±3.7            | 0.007        |
| ICD                             | 142 (40.7)  | 40 (24.7)       | 102 (54.6)         | <0.0001      |
| Hypertension                    | 118 (33.2)  | 80 (48.5)       | 38 (20.0)          | <0.0001      |
| Comorbidities                   | 193 (62.3)  | 90 (67.2)       | 103 (58.5)         | 0.12         |
| Body mass index                 | 28.1±5.2    | 28.9±4.9        | 27.0±5.3           | 0.003        |

#### Echocardiography

| Max wall thickness               | 20.1±5.4    | 18.8±4.0        | 21.2±6.2           | <0.0001      |
| Posterior wall thickness         | 11.3±2.7    | 11.7±2.2        | 10.8±2.9           | 0.002        |
| Septal morphology                |             |                 |                    |              |
| Asymmetric                      | 282 (84.4)  | 119 (76.7)      | 163 (91.1)         | 0.001        |
| Apical                          | 34 (10.2)   | 25 (16.1)       | 9 (5.0)            |              |
| Concentric                      | 18 (5.4)    | 11 (7.1)        | 7 (3.9)            |              |
| LVOTO ≥30 mm Hg at rest          | 126 (36.0)  | 70 (43.5)       | 56 (29.6)          | 0.007        |
| Maximum gradient, mm Hg         | 29.0±41.1   | 38.3±47.4       | 24.2±35.8          | 0.002        |
| Severe LVH ≥30 mm               | 23 (6.6)    | 3 (1.9)         | 20 (10.6)          | 0.001        |
| LVEDD                           | 44.8±7.1    | 45.7±6.8        | 43.9±7.2           | 0.02         |
| LVESD                           | 27.9±6.8    | 28.6±6.3        | 27.1±6.8           | 0.05         |
| LA size                         | 44.2±8.5    | 45.0±8.9        | 43.8±8.4           | 0.22         |

#### Cardiac MRI (n=66)

| Presence of LGE                 | 52 (77.6)   | 27 (72.3)       | 25 (83.3)          | 0.31         |

AF indicates atrial fibrillation; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; LA, left atrial; LGE, late gadolinium enhancement; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; LVH, left ventricular hypertrophy; LVOTO, left ventricular outflow tract obstruction; MRI, magnetic resonance imaging; SCD, sudden cardiac death; and VT, ventricular tachycardia.
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cardiovascular death (heart failure, stroke, and SCD), cardiac transplant, aborted cardiac arrest, and ventricular fibrillation ICD shocks compared with nonfamilial HCM (15 events; 5 SCD, 2 transplant; 6 aborted cardiac arrest, 2 heart failure deaths; mean±SE event-free survival to age 74.0±0.9 years) throughout their lifetime until 80 years (log-rank \( P =0.04 \); Figure 3D), again highlighting the relatively benign clinical course.

Clinical Score to Predict Nonfamilial HCM Status

To better understand the pretest probability of nonfamilial HCM, we compared the performance of 2 established genotype prediction models and our above-mentioned multivariate analyses (referred to as Sydney genotype prediction score; Table 2) in probands with no family history of HCM. Mean predicted probabilities were higher among sarcomere-positive probands for the Toronto (0.31±0.15 versus 0.18±0.11; \( P <0.0001 \)), Mayo (0.38±0.19 versus 0.24±0.15; \( P <0.0001 \)), and Sydney scores (0.45±0.16 versus 0.32±0.15; \( P <0.0001 \)). Receiver operating characteristics curves demonstrated good performance of the scores in predicting a positive genotype among those with no family history, with area under the curve’s ranging from 0.71 (Mayo and Sydney scores) to 0.75 (Toronto score; Figure 4A). A cutoff for the Toronto score predicted probabilities was established at \( \leq 0.25 \), giving a sensitivity of 75% and specificity of 63%, equating to a score of \( \leq 2 \) indicating low risk and >2 indicating high risk of a positive genotype (Figure 4B and 4C).

Further improvement for positive genotype prediction could be achieved by incorporating both the binary Toronto score (high/low) and the number of adult children the proband has (<2 or \( \geq 2 \) adult children). A high Toronto score (adjusted OR, 3.83; 95% CI, 1.94–7.55; \( P =0.0001 \)) and <2 adult children (adjusted OR, 2.20; 95% CI, 1.12–4.35; \( P =0.023 \)) were both significant and independent predictors of a positive genotype, giving an area under the curve of 0.72 and adjusted

Table 2. Unadjusted and Adjusted Odds Ratios for Factors Associated With Nonfamilial (Using Stringent Family Criteria) Versus Sarcomere-Positive HCM (Sydney Genotype Score)

|                                | Univariate Analyses | Multivariate Analyses,* Sydney Genotype Score |
|--------------------------------|---------------------|-----------------------------------------------|
|                                | OR 95% CI  PValue    | OR 95% CI  PValue                              |
| Age, y                         | 1.05    1.03–1.07 <0.0001 | 1.04    1.02–1.06 0.0001                     |
| Male sex                       | 1.72    1.05–2.80 0.03  | 1.96    1.11–3.45 0.02                        |
| Body mass index                | 1.09    1.04–1.15 0.001 |                                             |
| Nonsustained VT                | 0.64    0.37–1.11 0.12  |                                             |
| SCD event                      | 0.43    0.19–0.99 0.047 |                                             |
| Hypertension                   | 4.53    2.71–7.56 <0.0001 | 2.80    1.57–5.00 0.0005                     |
| Comorbidities                  | 1.42    0.84–2.38 0.19  |                                             |
| Maximum LWT, mm                | 0.91    0.86–0.96 0.0002 |                                             |
| Posterior WT                   | 1.12    1.02–1.23 0.018 |                                             |
| Nonasymmetrical septal morphol | 3.54    1.81–6.92 0.0002 | 3.41    1.64–7.08 0.001                      |
| LV outflow tract obstruction   | 1.50    1.02–2.46 0.11  |                                             |

CI indicates confidence interval; HCM, hypertrophic cardiomyopathy; LV, left ventricular; LWT, left ventricular wall thickness; OR, odds ratio; SCD, sudden cardiac death; and VT, ventricular tachycardia.

* C statistic for the area under the curve (AUC) for this model was 0.77, and R square was 0.20. Intercept −2.12.

Table 3. Quantitative Family History Characteristics of Nonfamilial Versus Sarcomere-Positive HCM Probands

|                                | Nonfamilial HCM, mean±SD | Sarcomere-Positive, Negative FHx | OR (95% CI) Adjusting for Proband Age | PValue | Sarcomere-Positive, Total group | OR (95% CI) Adjusting for Proband Age | PValue |
|--------------------------------|---------------------------|----------------------------------|--------------------------------------|--------|-------------------------------|--------------------------------------|--------|
| Total family size (proband and 1st-degree relatives \( \geq 18 \) y) | 7.6±2.5                   | 6.4±2.1                          | 1.12 (0.97–1.30)                     | 0.14   | 6.6±2.5                       | 1.00 (0.90–1.11)                     | 0.97   |
| Total living family size (proband and 1st-degree relatives \( \geq 18 \) y) | 5.7±2.3                   | 5.7±2.3                          | 1.10 (0.95–1.27)                     | 0.21   | 5.5±2.1                       | 1.01 (0.91–1.12)                     | 0.87   |
| Number of parents alive (0, 1, and 2) | 0.6±0.8                   | 1.0±0.9                          | 0.93 (0.57–1.53)                     | 0.78   | 1.1±0.8                       | 0.86 (0.59–1.25)                     | 0.43   |
| Number of siblings \( \geq 18 \) y and alive | 2.3±1.8                   | 2.3±1.8                          | 1.0 (0.85–1.20)                      | 0.95   | 2.2±1.7                       | 1.02 (0.90–1.17)                     | 0.73   |
| Number of children \( \geq 18 \) y and alive | 1.8±1.4                   | 1.0±1.3                          | 1.38 (1.04–1.82)                     | 0.02   | 1.2±1.4                       | 1.03 (0.85–1.26)                     | 0.73   |
| Total number of 1st-degree relatives \( \geq 18 \) y clinically screened | 2.7±1.9                   | 2.6±1.8                          | 1.01 (0.86–1.18)                     | 0.92   | 3.0±1.8                       | 0.89 (0.79–1.01)                     | 0.08   |

Data as odds ratios (OR) and 95% confidence intervals (CI) adjusting for proband age as a confounder. CI indicates confidence interval; FHx, family history; HCM, hypertrophic cardiomyopathy; and OR, odds ratio.
$R^2=0.19$ (compared with area under the curve of 0.69 and adjusted $R^2=0.17$ using Toronto score alone). While giving only modest improvement in prediction, this does serve to better refine genetic testing yield. The proportion of positive genotypes identified was calculated among those with no family history to represent genetic yield at each of these extremes. This serves as a guide for better understanding pretest probability of a gene result among those without a family history of disease (Figure 5). Those with the least chance of a positive genotype (ie, nonfamilial HCM) have a low Toronto score and ≥2 children, with a pickup rate of 13%, while the greatest yield were those with high Toronto score and <2 adult children with a pickup of 56%.

**Discussion**

We have identified that HCM probands with no overt family history of HCM and no identifiable genetic cause (ie, nonfamilial HCM) have several clinical features that suggest a different underlying pathogenesis. This subgroup comprises 40% of all HCM and has a more favorable clinical course, including later presentation and better event-free survival from major cardiovascular events. Nonfamilial HCM patients are more likely to be male, of older age, with nonasymmetric hypertrophy, and coexistent hypertension. Our findings bring into sharp focus the need to revisit current diagnostic algorithms. Furthermore, characterization of the nonfamilial HCM subgroup has direct implications for management of HCM patients and specifically clinical surveillance strategies in families.

The existence of a clinically distinct nonfamilial form of HCM without traditional autosomal dominant inheritance is a major finding of the current study. The concept of an HCM patient subgroup without a Mendelian cause is supported by strong observational data that those with indeterminate gene results are also statistically more likely to have no family history of disease. Numerous studies have consistently reported a greater genetic yield in those probands with familial disease. 8,18,19,29–31 Indeed, one study showed...
that sarcomere-positive patients have an increased risk of cardiovascular events and progression to New York Heart Association functional class III-IV, compared with their gene-negative counterparts. In the current study, we included comprehensive quantitative pedigree data from our consecutive HCM patient series with ≤24 years follow-up. A unique aspect of our clinics is the strong family-based approach to care, with integrated cardiac genetic counseling alongside cardiac care. Based on these family data, we have shown that where there is a negative family history, the number of first-degree adult relatives screened in a family had no correlation with genetic yield. The term nonfamilial HCM would not exclude the possibility of the underlying cause being a combination of complex gene–environment interactions, but this would not infer Mendelian inheritance risks.

The clinical characteristics observed in our nonfamilial HCM patients are likely to be confounded by age, given the later age of disease onset compared with sarcomere-positive HCM. The nonfamilial HCM patients were almost 15 years older. Importantly, we have shown that nonfamilial HCM patients have a greater mean body mass index, and almost 50% have hypertension. In the multivariable analyses, hypertension remained an independent risk factor even after adjusting for age, and given the known correlation with LV hypertrophy, albeit to a lesser degree than is observed in diagnostic HCM, this is a prime candidate for better defining disease mechanisms in this group. Importantly, all HCM patients in this study were clinically diagnosed in a specialist HCM center and do not have the morphological appearance of LV hypertrophy related to hypertension. This does not undermine the
importance of hypertension as a contributor to the nonfamilial HCM phenotype. Investigation of the mechanisms underpinning disease in nonfamilial HCM will provide a greater evidence base for these differences between nonfamilial and sarcomere-positive HCM.

We found ≈30% of probands with no family history had a positive gene result. The reason for this lack of affected relatives is likely to have multiple causes, including the trend to smaller family sizes, variable penetrance of particular variants, and de novo events. Of interest, after adjusting for proband age, we demonstrated family size to be the same among those with and without a positive gene result. The exception to this was the number of adult children of the proband, with nonfamilial HCM probands being much more likely to have ≥2 children without overt evidence of disease (note that these children had not necessarily been clinically screened). We also investigated the distribution of genes in sarcomere-positive probands with and without a family history of disease, given some genes might be more penetrant; however, this showed no statistical difference. De novo events can be difficult to confirm, but in those cases where parental samples could be obtained, we observed this rarely, consistent with previous data.8

Our findings have important clinical implications relevant to the evaluation and management of HCM patients, and specifically the nonfamilial HCM subgroup. A revised clinical pathway for HCM is summarized in Figure 5. A comprehensive 3-generation pedigree should be considered a critical component of clinical investigation of HCM, with a positive family history that demonstrates the inherited nature of disease being supportive of current management approaches. This includes the need for ongoing periodic clinical surveillance of family members, high pretest probability of a positive genetic result that enables a greater degree of certainty in interpretation of genetic variants, and need for close cardiology review to mitigate future clinical risks. Where the family history is negative, further stratification of genetic yield can be determined by clinical and pedigree factors (Figure 5).

Based on our data, we would suggest that genetic testing of established HCM genes is required for all probands, regardless of genetic yield, though some centers may need to prioritize because of a lack of resources. We emphasize that designation of nonfamilial HCM should only be applied to those probands with a negative family history and negative genetic test. A positive gene result confirms sarcomere-positive HCM, which means that first-degree relatives have a 50% risk of carrying the family mutation, and would be advised to undertake further clinical or genetic evaluation as per current guidelines. Conversely, a negative gene result in the proband indicates a more benign clinical course and likely much lower risk in other family members after consideration of alternative diagnoses and phenocopies. Our findings suggest that different diagnostic criteria should be applied to nonfamilial HCM and propose first-degree relatives have clinical screening at least once in adulthood, but ongoing clinical surveillance could be ceased or undertaken less frequently.

Potential limitations of this study include the inability to clinically screen every first-degree relative among nonfamilial HCM cases; on average, 2 to 3 adult relatives underwent clinical screening. In addition, septal morphology had historically been recorded as asymmetrical, apical, or concentric; therefore, further subanalysis of other subtypes such as sigmoid could not be performed. Further research is necessary to determine how many family members should be clinically screened to be confident that a family history is truly negative, though our data suggest that 2 to 3 may be adequate.

Figure 5. Revised clinical pathway incorporating nonfamilial hypertrophic cardiomyopathy (HCM) subgroup.
Conclusions

HCM is an autosomal dominant disease caused by variants in sarcomere genes. We have now shown in 40% of clinical HCM that a nonfamilial disease subgroup exists. This nonfamilial HCM subgroup has a more benign clinical course and better event-free survival from cardiac events compared with sarcomere-positive HCM. These findings further emphasize the value of a family history and genetic testing. This has important implications for clinical management pathways in HCM patients and demonstrates a need to revisit current diagnostic guidelines. Efforts to delineate disease subgroups rather than accepting the marked phenotypic heterogeneity as a hallmark feature of HCM will allow greater capacity to provide personalized evidence-based care to patients and their families.

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Disclosures

None.

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