10.1161/CIRCULATIONAHA.118.038846

Yield of Clinical Screening for Hypertrophic Cardiomyopathy in Child First-Degree Relatives: Evidence for a Change in Paradigm

Running Title: *Norrish et al.; Screening for Childhood Hypertrophic Cardiomyopathy*

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10.1161/CIRCULATIONAHA.118.038846

Abstract

Background: Hypertrophic Cardiomyopathy (HCM) is a heritable myocardial disease with age related penetrance. Current guidelines recommend clinical screening of relatives from the age of 10 years onwards but the clinical value of this approach has not been systematically evaluated.
Methods: Anonymized, clinical data were collected from children referred for family screening between 1994-2017 following diagnosis of HCM in a first-degree relative.
Results: 1198 consecutive children (aged ≤ 18 years) from 594 families underwent serial evaluation [median 3.5 years (IQR, 1.2-7)]; 32 individuals met diagnostic criteria at baseline (median maximal LV wall thickness (MLVWT) 13mm (IQR, 8-21mm)) and 25 additional patients developed HCM during follow up. Median age at diagnosis was 10 years (IQR 4-13); 44 (72%) were 12 years or younger. Median age of affected patients at last follow up was 14 years (IQR 9.5-18.2). A family history of childhood HCM was more common in those patients diagnosed with HCM (n=32, 56%, VS n=257, 23% P <0.001). 18 patients (32%) were started on medication for symptoms, 2 (4%) underwent a septal myectomy, 14 (25%) received an implantable cardioverter defibrillator, 1 underwent cardiac transplantation, 2 had a resuscitated cardiac arrest and 1 died following a cerebrovascular accident.
Conclusions: Almost 5% of first-degree child relatives undergoing screening meet diagnostic criteria for HCM at first or subsequent evaluations, with the majority presenting as pre-adolescents; a diagnosis in a child first-degree relative is made in 8% of families screened. The phenotype of familial HCM in childhood is varied and includes severe disease, suggesting that clinical screening should commence at a younger age.

Key Words: Child; screening; genetics; sudden death; cardiomyopathy

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Clinical Perspective

What is new?

- A diagnosis of Hypertrophic Cardiomyopathy (HCM) is made in almost 5% of first-degree childhood relatives from 8% of families
- The majority of diagnoses (72%) are made in pre-adolescence
- A diagnosis of HCM was more likely in the context of a family history of childhood onset disease

What are the clinical implications?

- The phenotype of familial HCM in childhood is varied and includes severe disease, suggesting that clinical screening should commence at a younger age.

Introduction

Hypertrophic cardiomyopathy (HCM) is a heritable myocardial disease characterized by left ventricular hypertrophy (LVH) unexplained by abnormal loading conditions. It is rare in childhood, with an estimated annual incidence of 0.24-0.47 per 100,000 [1-3] and prevalence of 2.7 per 100,000[1]. The etiology of childhood HCM is heterogeneous and includes inborn errors of metabolism, malformation syndromes and neuromuscular disease [4, 5]. However, the majority of disease in childhood is caused by mutations in cardiac sarcomere protein genes [6,7], which are inherited as autosomal dominant traits but exhibit variable and age-related penetrance[8]. Previous studies have suggested that LVH in familial and sarcomeric HCM usually develops during adolescence[4, 5, 9, 10] and current clinical practice guidelines [11, 12] recommend family screening for first degree child relatives from the age of 10 years onwards. However, the clinical value of this approach has not been systematically assessed. The aim of this study was to describe the yield of clinical screening for HCM in childhood and adolescent first degree relatives in a large referral center population.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Patients

All patients aged 18 years and younger referred between 1994 and 2017 to Great Ormond Street Hospital Center for Inherited Cardiovascular Diseases for family screening following a diagnosis of HCM in a first-degree relative were included in the study. Children referred for investigation of symptoms, with a prior diagnosis of HCM, or with a family history of non-

sarcomeric HCM (including a malformation syndrome, neuromuscular disease or inborn error of metabolism) were excluded.

Clinical evaluation

All patients underwent detailed evaluation at baseline and during follow up (12 to 24 monthly during pre-adolescent years and 6 to 12 monthly during adolescent years) until they were transitioned to adult services (at the age of 18 years) or the end of the study period. Anonymized, non-invasive clinical information was collected from baseline clinical evaluation, follow up and last clinical review, including: demographics; symptoms; medical therapy; physical examination; family history; resting and ambulatory electrocardiography (ECG); and two dimensional (2D), Doppler and color transthoracic echocardiography. A diagnosis of HCM was made if left ventricular wall thickness was greater than two standard deviations (SD) above the body surface area (BSA)-corrected population mean (> z-score +2), which could not be solely explained by abnormal loading conditions, or in accordance with published criteria for familial disease[11].

Echocardiographic measurements were made according to current guidelines[13]. Specifically, end-diastolic left ventricular (LV) wall thickness was measured by 2D echocardiography in the parasternal short-axis views in four places at the level of the mitral valve and papillary muscles (anterior and posterior septum, lateral and posterior wall) and in two places at apical level (anterior and posterior septum)[11]. Maximum LV wall thickness (MLVWT) was defined as the greatest thickness in any single segment. Left ventricular outflow tract (LVOT) obstruction was defined as an instantaneous peak Doppler LVOT pressure gradient ≥ 30mmHg at rest[11]. A hemodynamically significant gradient was considered to be an instantaneous peak Doppler gradient ≥ 50mmHg[14]. LV diastolic

dysfunction was assessed to be present if two out of four variables used to assess diastolic function were out of normal range for age and body surface area (annular E' velocity, septal E' velocity, average E/E' ratio, LA volume)[15]. 12 lead ECGs for patients meeting diagnostic criteria for HCM were analyzed by one observer (G.N.) for the following: QRS axis, Sokolow-Lyon voltage criteria for left ventricular hypertrophy (V1 + RV5/6 >35mV), abnormal Q waves and repolarization abnormalities. Non-sustained ventricular tachycardia (NSVT) during ambulatory ECG monitoring was defined as three or more consecutive ventricular beats at a rate of greater than 120 beats/min with a duration of less than 30 seconds[11].

Genetic testing

Sequencing methods varied according to year, panel and the clinical laboratory conducting the testing. Before 2011, targeted testing of HCM genes (4-10 genes) was performed by direct Sanger sequencing. Next generation sequencing (NGS) were available from 2011 onwards. For the purpose of analysis, NGS panels were described as small (≤ 21 genes) or expanded (> 21 genes). The genes included in panels varied depending on the year and clinical laboratory conducting the testing.

Data were collected from those families in whom genetic testing had been performed, including: date of testing, genetic testing strategy and variants identified.

The pathogenicity of all reported variants was re-classified by the authors according to the American College of Medical Genetic classification[16].

Statistical analysis

All statistical analyses were performed using STATA (Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). Body surface area was calculated from height and

weight[17]. MLVWT measurements are expressed in millimeters and as z-scores relative to the distribution of measurements versus body surface area in normal children[18]. Normally distributed continuous variables are described as mean +/- standard deviation with two group comparisons conducted using Student t test. Skewed data are described as median (interquartile range, IQR) with two group comparisons performed using Wilcoxon rank sum. To determine the association between relevant predictors, univariable analysis was performed using Chi Squared test or Fishers exact test. A p value of <0.05 was accepted as significant for all analyses. Locally weighted scatterplot smoothing (Lowess) was performed for all line graphs.

IRB approval: This study was approved by Great Ormond Street Hospital/ University College London Institute of Child Health Research and Development Office.

Results

1198 consecutive pediatric first-degree relatives from 594 families were referred for clinical family screening over the study period. The number of patients evaluated per calendar year is shown in *supplementary figure 1*. Mean age at referral was 7.9 years (+/-4.7, range 0-18 years). 964 patients (80%) were 12 years or younger at baseline evaluation. 387 patients (32%) were transitioned to adult services by the end of the study period.

Yield of clinical screening

Over a median follow up of 3.5 years (IQR, 1.2-7), 57 patients (4.7%) were diagnosed with childhood HCM from 48 unrelated families. A diagnosis in a first-degree child relative was made in 8.1% of families screened. The yield of clinical screening did not differ by era of screening **(Table 1).** Age at diagnosis was under 1 year in 6 patients (11%), 1-6 years in 15

(26%), 7-12 years in 20 (35%) and above 12 years in 16 (28%) (Figure 1b). Median age at diagnosis was 10 (IQR 4-13). 32 individuals met diagnostic criteria at baseline and 25 additional patients developed HCM during follow up. The age at baseline evaluation did not differ between these groups [baseline diagnosis (n=32) median age 5 years, IQR 1-11.5 vs diagnosis during follow up (n=25) median age 5, IQR 4-9; p=0.872]; however, those diagnosed during follow up were older at the time of diagnosis (median 12 years, IQR 9-14, compared to median 6 years IQR 1-11.5; p=0.02). **Table 1** compares the demographics of those with and without a diagnosis of HCM. Patients with a childhood diagnosis were more likely to have a family history of childhood HCM (n=32, 56%, VS n=257, 23% P <0.001). Of this group, 148 (12.3%) had an affected pediatric sibling as one of their first-degree relatives.

Genetic testing

The genetic testing strategy for the whole cohort is shown in **Figure 1a**. In brief, genetic testing was performed in 192 families (32%), with a pathogenic or likely-pathogenic sarcomeric variant identified in 122 (64%). Of variants previously classified as pathogenic/likely pathogenic, following ACMG re-classification; 87 variants remained pathogenic/likely pathogenic and 24 were re-classified (variant of unknown significance n=22, benign variant n=2). 7 variants previously classified as VUS were re-classified to pathogenic/likely pathogenic *(supplementary table 1).* The genetic testing strategy in the 57 pediatric patients diagnosed through family screening is shown in **Figure 1b.** In brief, genetic testing for sarcomeric mutations was performed in 39 individuals (68%) (40 families (83%)), identifying a pathogenic sarcomeric variant in 27 (69%) individuals: MYH7 n=18; MYBPC3 n=7; TPM1 n=1; MYBPC3 + TNNT2 n=1). 22 patients (39%) underwent predictive testing for a familial sarcomeric gene variant and 17 (30%) underwent gene panel testing. The

sequencing method and number of genes tested in the genetic index case was as follows: Sanger sequencing (n=9, 22.5%); small NGS panel (n=13, 32.5%); expanded NGS panel (n=9, 22.5%); unknown (n=9, 22.5%). 16 families underwent genetic testing with no pathogenic variant identified; Sanger sequencing (n=6), small NGS panel (n=3), extended NGS panel (n=6), unknown panel (n=1). The genetic testing strategy by era is shown in *supplementary table 2.* The yield of genetic testing by year of presentation is shown in *supplementary figure 2.* Median age at diagnosis for sarcomeric mutation carriers was 6 (IQR 3.75-10); twenty-one (78%) were under 10 years.

Phenotype at baseline of patients meeting diagnostic criteria for HCM

Table 2 describes the baseline clinical features of the 57 patients diagnosed with HCM through clinical screening. Of 32 patients meeting diagnostic criteria for HCM at baseline, four (13%) reported previous cardiac symptoms [chest pain (n=2), dyspnea (n=2)]. Twenty-eight (88%) had asymmetric septal hypertrophy (ASH) with a median MLVWT of 13mm (IQR, 8-21mm) and mean Z score +8.9 (SD +/-5.4); no patient had a MLVWT ≥ 30mm. Three patients (6%) had resting LVOT obstruction. Twenty-eight patients (88%) had abnormalities on a resting 12-lead ECG.

Of 25 patients not meeting diagnostic criteria at baseline assessment but who developed HCM during follow up in childhood, 14 (56%) had abnormalities on a resting 12 lead ECG and three had non-diagnostic echocardiographic abnormalities (impaired diastolic function n=1, incomplete systolic motion (SAM) of the mitral valve n=2) at baseline evaluation.

Disease progression in patients meeting diagnostic criteria for HCM

Patients with a diagnosis of HCM were followed up for a median of 7.3 years (IQR 2.7-12.8

years). Nine patients (16%) had less than 1 year follow up. For 48 patients in whom serial echocardiographic measurements were available, MLVWT increased at a median rate of 0.8mm/year (range -0.7 - 3.9mm/year, IQR 0.4-1.6mm) **Figure 2**. At last clinical follow up, 52 patients (91%) had ASH with a median MLVWT of 17mm (IQR12.5-24.5). Five patients had a maximal wall thickness ≥ 30mm. Median LVOT gradient was 9 (IQR 6-13); two patients had LVOT obstruction at rest. Only 3 patients (5%) had no abnormalities on 12 lead ECG.

Clinical outcome of patients meeting diagnostic criteria for HCM

During clinical follow up, 17 patients (30%) reported cardiac symptoms (palpitations n=6, dyspnea n=4, chest pain n=5 and pre-/syncope n=3) and eighteen (32%) were started on medications. Indications for starting medical therapy are described in **Table 3**. Two patients underwent a myectomy and 4 an electrophysiology study. Fourteen patients (25%) received an ICD; two for secondary prevention following a resuscitated cardiac arrest at the age of 14 and 25 years, respectively, and 12 for primary prevention of malignant arrhythmias (**Table 3)**. Over a median follow up of 5.7 years (IQR 2.1-6.7), 1 patient received multiple appropriate therapies (aged 26 years); 1 patient received inappropriate ICD therapy and was found to have a lead fracture (aged 20 years); 1 patient developed infective endocarditis with ICD lead vegetation's (aged 22 years); and two further patients required ICD lead replacement due to somatic growth. Fifty-eight patients (98%) were alive and well at last clinical follow up with a median age of 14 years (IQR 9.5-18.2); 16 patients (28%) were above the age of 18 years. One patient died as a result of a cerebrovascular accident at the age of 24 years. One patient progressed to end-stage HCM necessitating cardiac transplantation at the age of 15 years. In this family, mitochondrial disease was initially suspected as the phenotype included pre-

excitation on 12-lead resting ECG, recurrent supraventricular and ventricular arrhythmias, retinitis pigmentosa and early progression to end-stage disease in the patient and her mother. However, genetic testing on an expanded NGS panel and metabolic investigations including a muscle biopsy did not identify an underlying etiology.

Discussion

This study is, to our knowledge, the first to describe the yield of clinical screening for HCM in first-degree relatives in a large unselected consecutive childhood cohort. The results suggest that clinical screening for HCM in first-degree relatives should be considered earlier than recommended by current international guidelines.

Clinical yield of screening during childhood

Cascade family screening to identify asymptomatic individuals is widely accepted as an important part of HCM management, but there are no data on the clinical yield of screening in adult or pediatric HCM relatives. The present study demonstrates that clinical screening for HCM in childhood results in a diagnosis in almost one tenth of families, with high variability in the age at which a phenotype develops. In the absence of a malignant family history, symptoms or involvement in competitive sports, current guidelines do not recommend screening during childhood below the age of 10 years. These recommendations are largely derived from expert opinion based on reports that; development of a phenotype is rare during childhood; progression of LVH is most commonly seen during adolescence [9]; and adverse events occur rarely in childhood[4, 5]. However, we have shown that, in most cases where a diagnosis is made in childhood, this occurs in pre-adolescence. Furthermore, although patients with a diagnosis made through screening in childhood were more likely to have a family

history of childhood disease, this only accounts for half of patients with early-onset disease. The results of this study represent a paradigm shift and support the notion that, if it is accepted that screening is important, consideration should be given to commencing screening for familial disease at a younger age.

Importance of an early diagnosis

Early diagnosis of HCM through family screening enables appropriate treatment to be instigated promptly. Although most patients undergoing family screening are asymptomatic, symptoms attributable to HCM are often non-specific meaning that delays in management are common, as cardiac investigations may not be initially considered. Early diagnosis also facilitates surveillance for disease complications, such as malignant arrhythmias, which may occur even in asymptomatic individuals. In this cohort, diagnosis resulted in a change in management (medication for symptoms, ICD implantation or myectomy) for over one third of patients. Of note, this included one patient who received appropriate ICD therapies having undergone primary prevention ICD implantation. In contrast, 2 patients without an ICD had an out of hospital resuscitated cardiac arrest, highlighting the challenges of risk stratification in childhood HCM. Importantly, recent animal data have shown that novel compounds may have a role in preventing disease expression in HCM[19]. In the future, early detection of these patients through family screening will be important to identify a group of patients likely to benefit from such therapies.

Progression of familial hypertrophic cardiomyopathy during childhood

Our understanding of the progression of familial disease in childhood remains incomplete. Maron et al [9]described the progression of left ventricular hypertrophy in a small childhood cohort (39 patients) and found that increases in wall thickness were more frequently seen in

adolescence. However, this study contained small numbers of pre-adolescent patients (n=10) of whom 40% had pre-existing LVH. In comparison, most patients with childhood disease in our cohort were first evaluated under the age of 12 years and the majority developed LVH in pre-adolescence. Following diagnosis, increases in the absolute and body-surface area corrected maximal wall thickness occurred throughout childhood. Interestingly, progression of LVH in patients diagnosed later in childhood reflected that previously described, with increases in wall thickness occurring during adolescence. This suggests that earlier screening identifies two distinct groups: a substantial minority who have evidence of HCM in early childhood with a natural history similar to that previously described but shifted to the left, and a second, larger group in whom the disease may not develop until adulthood. Several patients in our cohort reached a peak MWT during childhood, with regression of hypertrophy in early adulthood, and one patient developed end-stage disease requiring a heart transplant during childhood. Progression to a dilated, hypokinetic 'burnt out' phase is exceedingly rare in non-metabolic childhood HCM [20] and extensive genetic testing failed to identify a sarcomeric mutation in this patient, suggesting an alternative etiology.

Genetic testing

Although the impact of genetic testing was not the focus of this study, our findings raise the important question of whether predictive genetic testing may be a more cost-effective way to screen pediatric relatives of HCM than clinical screening [21]. In routine clinical practice, however, the family genotype may not always be known. In this study, genetic testing over the study period was not systematic and was primarily performed on a research basis[7, 22], explaining the relatively low proportion of genotyped families in this cohort. Nevertheless, in those children with a diagnosis of HCM, over two thirds (68%) have undergone genetic

testing identifying a pathogenic sarcomeric variant in 69%. The increasing use of predictive testing since 2016 reflects the more widespread availability of genetic testing in both pediatric and adult cardiomyopathy services. This study did not attempt to investigate the penetrance of sarcomeric mutations during childhood but does provide further evidence that sarcomeric disease can present in younger children [6, 7].

Limitations

Due to the retrospective nature of the study and the fact that many families were seen prior to the availability of widespread genetic testing, the clinical yield of screening childhood first degree relatives reported in this study is likely to be an underestimate of the true penetrance of childhood sarcomeric disease, as the cohort necessarily contains both genotype positive and negative individuals. This reflects real world clinical practice, where the genotype status of a child is often unknown. This study only included data on children referred for screening following a diagnosis of HCM in a first-degree relative and the findings may not be applicable to the general pediatric HCM population. In particular, the data on disease progression relates to patients with childhood familial HCM diagnosed through clinical screening and as such may not be generalisable to those presenting with symptoms or as diagnosed as an incidental finding. Further work to explore the age-related, gene-related and mutation-specific penetrance of sarcomeric disease in childhood is needed.

Conclusions

In a large, unselected consecutive childhood cohort, almost 5% of first-degree child relatives undergoing screening meet diagnostic criteria for HCM at first or subsequent evaluations, with the majority presenting as pre-adolescents. Furthermore, a diagnosis of HCM in at least one pediatric first-degree relative is made in 8% of families screened. A diagnosis of HCM was more

likely in the context of a family history of childhood onset disease. The phenotype of familial HCM in childhood is varied and includes severe disease, suggesting that clinical screening should commence at a younger age

Acknowledgments

University College London & St. Bartholomew's Hospital (London EC1A 7BE, United Kingdom) and Great Ormond Street Hospital for children (London, WC1N 4JH, United Kingdom) is a member of ERN GUARD-HEART (European Reference Network for Rare and Complex Diseases of the Heart; http://guardheart.ern-net.eu).

Sources of Funding

This work was supported by the British Heart Foundation (grant number FS/16/72/32270) to GN and JPK. EF and JPK are supported by Max's Foundation and Great Ormond Street Hospital Children's Charity. This work is (partly) funded by the National Institute for Health Research Great Ormond Street Hospital Biomedical research Centre (NIHR GOSH BRC). The views expressed are those of the author(s) and not necessarily those of the National Health Service (NHS), the National Institute for Health Research (NIHR) or the Department of Health. Some of this work was undertaken at University College London (United Kingdom) and St. Bartholomew's Hospital (London, United Kingdom), which received a portion of funding from the United Kingdom Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme.

Disclosures

GN and JPK are supported by the British Heart Foundation (grant number FS/16/72/32270)

EF, EQ, HF, EL, EC, PME: None

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Table 1. Baseline demographics in patients with and without a diagnosis of HCM

		Whole cohort (n=1198)	Diagnosis made (n=57)	No diagnosis made (n=1141)	P value
Era of presentation	**1994-1999**	42 (3.5%)	5 (11.9%)	37 (88.1%)	0.228
	2000-2004	175 (14.6%)	10 (5.7%)	165 (94.3%)	
	2005-2009	279 (23.3%)	12 (4.3%)	267 (95.7%)	
	2010-2014	390 (32.6%)	15 (3.9%)	375 (96.2%)	
	2015+	312 (26%)	15 (4.8%)	297 (95.2%)	
Age at baseline clinical screening (mean, +/-SD, range)		7.88 +/-4.69 (0-18)	6.19 +/-4.51 (0-15)	7.97 +/-4.69 (0-18)	0.005
Age group at baseline clinical screening	**Infant**	91 (7.6%)	7 (12.3%)	84 (7.4%)	
	1-6years	395 (33%)	27 (47.4%)	368 (32%)	
	7-12 years	478 (40%)	18 (31.6%)	460 (40.3%)	
	13years+	239 (20%)	5 (8.8%)	229 (20.1%)	
Family history of childhood HCM		289 (24%)	32 (56%)	257 (22.5%)	<0.001
Family history of SCD		357 (31.3%)	25 (53.3%)	333 (30.7%)	0.058
Genetic testing performed in family		368	36 (63.2%)	332 (29%)	p<0.001
Length of follow up (months)		42 (13-84)	77 (31-134)	40 (13-81)	0.0018
Age at last FU		12.4 +/- 4.71	12.98 +/- 6.13	12.4 +/-4.63	>0.3593

Mann-Whitney used for length of follow up with all other continuous variables using the unpaired t-test.
Fisher's exact test used for all categorical variables.
HCM – hypertrophic cardiomyopathy; SCD – sudden cardiac death; FU – follow-up

Table 2. Baseline investigations for patients diagnosed with hypertrophic cardiomyopathy through family screening

			N (%)
Patients meeting diagnostic criteria at baseline investigation			32
ECG findings	**Abnormal ECG**		28 (88%)
		Abnormal axis	7
		LVH criteria	23
		Repolarisation abnormalities	23
		Q waves	9
		Atrial enlargement	5
Echocardiographic findings	**MWT (median, IQR)**		12.5 (8-21)
	MWT Z score (mean +/-SD)		8.9 (+/-5.4)
	Pattern of hypertrophy	**ASH**	28 (87.5%)
		Concentric	4 (12.5%)
	LVOT gradient (n=27), median IQR		7 (6 - 24)
	LVOT obstruction	**>30mmHg**	3 (11%)
		LVOT gradient >50mmhg	2 (7.4%)
	Diastolic impairment (n=24)		11 (45.8%)
	SAM		8 (25%)
Patients not meeting diagnostic criteria at baseline investigation			25
ECG findings	**Abnormal ECG**		14 (56%)
		Abnormal axis	3
		LVH criteria	1
		Repolarisation abnormalities	6
		Q waves	11
Echocardiographic findings	**No abnormalities**		22 (88%)
	SAM		2 (8%)
	Impaired diastolic function		1 (4%)

ECG – electrocardiogram; LVH – left ventricular hypertrophy; MWT – maximal wall thickness; ASH – asymmetric septal hypertrophy; LVOT – left ventricular outflow tract; SAM – systolic anterior motion of the mitral valve

Table 3. Management of patients with diagnosis of hypertrophic cardiomyopathy

			N (%)
Medication started			18 (32%)
Type of medication	**B-blockers**		17
	Disopyramide		5
	Calcium channel blocker		3
	Amiodarone		1
	Diuretics		1
	Angiotensin converter enzyme inhibitors		1
	Apixaban		1
Indication for medication	**symptoms**	**Chest pain**	1
		Pre-syncope/syncope	2
		Dyspnoea	4
		Palpitations	2
	Ambulatory ECG	**Ventricular ectopy**	2
		Sinus tachycardia	3
	LVOT obstruction		4
Implantable cardioverter defibrillator inserted			14 (25%)
Secondary prevention			2
Primary prevention	**Severe LVH**		2
	Severe LVH + FHx SCD		5
	Severe LVH + NSVT		2
	Severe LVH + GAD		1
	FHx SCD + abnormal BP response to exercise		2
Myectomy			2
Electrophysiology study	**Cavotricuspid isthmus ablation**		2
	Ablation accessory pathway		1
	Risk stratification (VT stim)		1

ECG – electrocardiogram; LVH – left ventricular hypertrophy; LVOT – left ventricular outflow tract; FHx – family history; SCD – sudden cardiac death; NSVT – non-sustained ventricular tachycardia; GAD – late gadolinium enhancement on cardiac magnetic resonance imaging (MRI); BP – blood pressure; VT – ventricular tachycardia

Figure Legends

Figure 1. Genetic testing in pediatric HCM patients

a) Genetic testing in patients referred for clinical screening

b) Genetic testing in patients diagnosed with hypertrophic cardiomyopathy through family screening

G+ = genetically tested and pathogenic sarcomeric mutation identified

G null = genetically tested and no pathogenic sarcomeric mutation identified

Figure 2. Progression of left ventricular hypertrophy during childhood

a) Change in absolute LVMWT during childhood in those patients diagnosed through clinical screening (n= 48)

b) Change in LVMWT Z score during childhood in those patients diagnosed through clinical screening (n= 48)

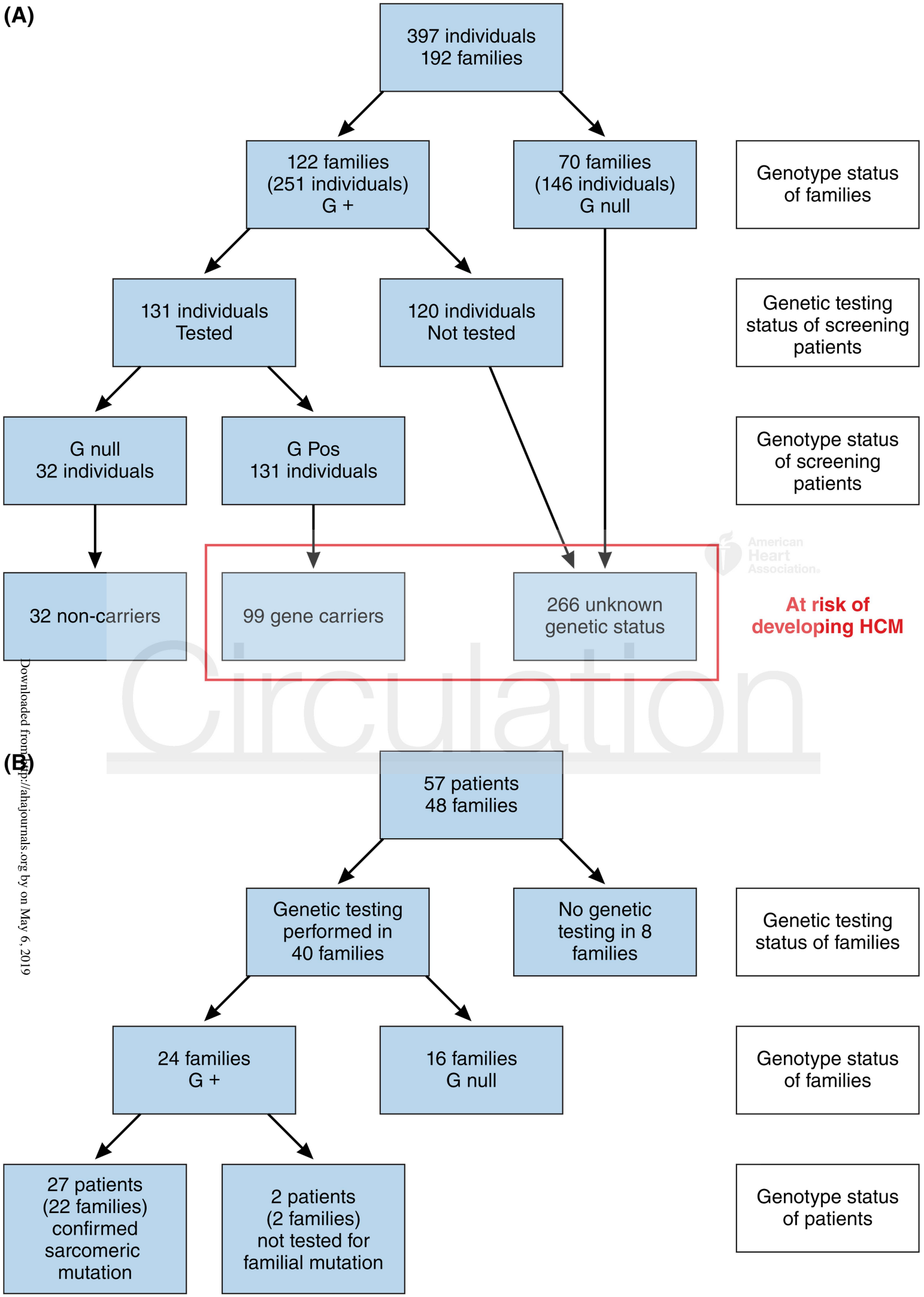
c) Change in absolute LVMWT during childhood in those patients diagnosed in pre-adolescence (12 years and under) (n=32)

d) Change in absolute LVMWT during childhood in those patients diagnosed in adolescence (13 years+) (n=16)

e) Change in absolute LVMWT during childhood in those patients diagnosed at baseline evaluation (n=32)

f) Change in absolute LVMWT during childhood in those patients diagnosed during follow up (n=25)

Connected dash line represents serial measurements from single patient. Red line represents Lowess locally weighted scatterplot smoothing.



b)

c)

d

e)