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ORIGINAL ARTICLE

Comprehensive Genetic Testing for Pediatric Hypertrophic Cardiomyopathy Reveals Clinical Management Opportunities and Syndromic Conditions

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Abstract

Hypertrophic cardiomyopathy (HCM) has historically been diagnosed phenotypically. Through genetic testing, identification of a molecular diagnosis (MolDx) is increasingly common but the impact on pediatric patients is unknown. This was a retrospective study of next-generation sequencing data for 602 pediatric patients with a clinician-reported history of HCM. Diagnostic yield was stratified by gene and self-reported race/ethnicity. A MolDx of HCM was identified in 242 (40%) individuals. Sarcomeric genes were the highest yielding, but pathogenic and/or likely pathogenic (P/LP) variants in syndromic genes were found in 36% of individuals with a MolDx, often in patients without documented clinical suspicion for a genetic syndrome. Among all MolDx, 73% were in genes with established clinical management recommendations and 2.9% were in genes that conferred eligibility for clinical trial enrollment. Black patients were the least likely to receive a MolDx. In the current era, genetic testing can impact management of HCM, beyond diagnostics or prognostics, through disease-specific guidelines or clinical trial eligibility. Genetic testing frequently can help identify syndromes in patients for whom syndromes may not be suspected. These findings highlight the importance of pursuing broad genetic testing, independent of suspicion based on phenotype. Lower rates of MolDx in Black patients may contribute to health inequities. Further research is needed evaluating the genetics of HCM in underrepresented/underserved populations. Additionally, research related to the impact of genetic testing on clinical management of other diseases is warranted.

Keywords Hypertrophic cardiomyopathy · Pediatrics · Genetic testing · Disparities

Abbreviations

HCM	Hypertrophic cardiomyopathy
MolDx	Molecular diagnosis
P/LP	Pathogenic/likely pathogenic

Introduction

In pediatric cardiology, genetic testing is now a well-accepted part of clinical practice, and for certain diseases results in both improved diagnostics and clinical management guidance when effectively implemented [1]. For patients with hypertrophic cardiomyopathy (HCM), 40–70% of affected adults have a causal pathogenic variant identified [2, 3]. However, the impact of a molecular diagnosis (MolDx) on the clinical management of this serious disease in pediatric patients is not well understood [4].

HCM is a serious and potentially fatal cardiomyopathy [5]. Although HCM remains a phenotypic diagnosis, it has

Partial data presented as a poster abstract at the virtual meeting of the American College of Medical Genetics and Genomics in March 2020 (originally scheduled to be in San Antonio and held virtually due to the COVID-19 pandemic). There has been no other prior presentation of study data.

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become increasingly possible with improved genetic testing to couple a HCM phenotype with a MolDx identifying a disease-causing variant responsible for either an isolated cardiomyopathy or a pleomorphic genetic syndrome that includes a cardiac defect [5]. Despite these advances, only a limited number of small studies have examined the clinical utility of genetic testing of children with HCM, and it is not known how many patients actually receive any clinical benefit from a MolDx, either in the form of genotype-specific management and therapies or newfound eligibility for enrollment in clinical trials [4, 6]. Additionally, genetic information related to HCM in non-White populations is lacking [7]. Disparities in access to a MolDx based on race or ethnicity may result in inequity in targeted therapeutics. We hypothesized that in the modern era, a MolDx can guide clinical management through disease-specific guidelines and/or clinical trial eligibility in pediatric HCM. We also sought to assess the impact of race/ethnicity on the ability to provide a MolDx.

Methods

Personal and family history information from testing requisition forms were reviewed for 602 patients under 18 years of age who were referred to Invitae for germline genetic testing for a clinician-reported history of HCM between 2013 and 2020. The cohort included eligible patients referred for genetic testing from multiple medical centers and community clinics nationwide. All patient data were de-identified before analysis under Western Independent Review Board protocol number 1167406.

Up to 150 genes were analyzed for each patient. Ordering clinicians typically selected standard gene panels for cardiomyopathies (e.g., Invitae Hypertrophic Cardiomyopathy Panel, Invitae Cardiomyopathy Comprehensive Panel, Invitae Arrhythmia and Cardiomyopathy Panel) all of which are customizable by the clinician (Supplementary Table 1). Adding more genes to a test did not increase cost. Sample types included blood and saliva. DNA was processed and subjected to paired-end sequencing on an Illumina next-generation sequencing platform [8]. Pathogenic/likely pathogenic (P/LP) variants, including single-nucleotide variants, small indels, and large deletions/duplications, such as copy number variants, along with other complex rearrangements were confirmed using orthogonal technology per Invitae standard operating practices [8]. MolDx was defined as either a P/LP variant in an autosomal dominant gene or two P/LP variants in an autosomal recessive (e.g., homozygotes).

Variants were subjected to clinical interpretation using Invitae's proprietary methodology, Sherloc, a refinement of the 2015 guidelines from the American College of Medical Genetics and Genomics and the Association for Molecular Pathology [9]. Only P/LP variants were included in the analysis of yield; gene-specific yields were calculated based on the number of patients tested on each gene. Diagnostic yield was stratified by gene, age at testing, and patient-reported race/ethnicity and MolDx results were reviewed for syndromic genes with pediatric presentation and further stratified by Rasopathy and non-Rasopathy syndromes as listed in Supplementary Table 2. To determine how a MolDx can impact clinical management beyond diagnostic or prognostic knowledge, we assessed clinical trial enrollment eligibility by searching clinicaltrials.gov using the following parameters: interventional, age < 18 years, gene name/genetic diagnosis used as part of recruitment, and status = recruiting (search conducted 5/13/2020). We also compared MolDx results with the availability of guideline-based recommendations to determine the impact of MolDx on precision therapeutic intervention. Finally, for probands with MolDx in syndromic genes, we reviewed all available clinical documentation submitted by ordering clinicians to assess whether the probands had syndromic presentations. Of note, submission of clinical information is optional, so not all patients had complete and available clinical information.

Results

Molecular Diagnosis of Isolated HCM

A total of 602 probands with a clinician-reported history of HCM were included (Table 1). Of these probands, 52% (313/602) had up to 60 genes sequenced on panels that included HCM genes and 42% (253/602) had up to 150 genes sequenced on the Invitae Arrhythmia and Cardiomyopathy Comprehensive Panel or a combination of other panels. The other 6% (36/602) underwent testing with more narrowly defined Noonan syndrome or RASopathy panels. P/LP variants were identified in 42% (255/602) of probands. A compendium of all P/LP variants observed is available in Supplementary Table 2. Of all probands with ≥ 1 P/LP variant, 94% (242/255) had findings consistent with a MolDx of HCM, accounting for an overall 40% (242/602) diagnostic yield for HCM. The other 13 probands harbored P/LP variants that did not result in a MolDx for HCM. Of these, 7 were carriers for variants in autosomal recessive genes associated with HCM and 6 had variants related to disorders that have not been associated with HCM in pediatric patients (5 had a MolDx and 1 was a carrier) (Fig. 1).

When stratified by self-reported race/ethnicity, the number of probands with P/LP variants identified exhibited a wide range: 65% (20/31) among Asian, 43% (103/239) among White, and 24% (21/89) among Black individuals. Among probands who self-identified as Hispanic, 46% (55/119) had a P/LP variant. The P/LP yield in Black

Table 1 Patient characteristics, $N = 602$

Characteristic	*n* (%)
Ages, years	
0–2	117 (19.4)
3–5	37 (6.1)
6–8	35 (5.8)
9–11	66 (11.0)
12–14	163 (27.1)
15–17	184 (30.6)
Gender	
Male	413 (68.6)
Female	189 (31.4)
Ancestry	
Ashkenazi Jewish	1 (0.2)
Asian	31 (5.1)
Black	89 (14.8)
Hispanic	119 (19.8)
Mediterranean	2 (0.3)
Multiple*	35 (5.8)
Native American	3 (0.5)
Unknown	83 (13.8)
White	239 (39.7)

*Multiple includes combinations of 2 or more of the following self-reported ancestries: Ashkenazi Jewish, Asian, Black, Hispanic, Mediterranean, Native American, Pacific Islander, and White

patients with HCM was 24%, significantly less than the 46% yield observed in the remainder of the cohort ($p = 0.0002$).

Consistent with prior reports, the highest yielding genes for a MolDx were the sarcomeric genes MYBPC3 (13%; 75/565 tested) and *MYH7* (12%; 66/565 tested). Among the 242 probands with a MolDx of HCM, 177 (73%) had a P/LP variant in a gene with established clinical management recommendations and 7 (2.9%) would be potentially eligible for clinical trial enrollment based in part on their germline test result (Table 2, Supplementary Table 3). Clinical management would not be impacted directly for the 7 probands found to be carriers of P/LP variants in recessive HCM genes, but these results could affect future reproductive considerations such as carrier screening for a P/LP variant in the same gene in partners or family members and their partners.

Multiple variants each independently consistent with a MolDx of HCM were reported in 5 probands (1%; 5/602), including one proband with multiple variants in *MYBPC3*. Two additional probands harbored a P/LP consistent with a MolDx of HCM as well as a P/LP in *TTR*, which is consistent with a MolDx of syndromic adult-onset HCM. One proband harbored a P/LP variant in MYBPC3 and a P/LP variant in KCNQ1 (a non-HCM gene), each consistent with a separate MolDx. Additionally, homozygous variants in GAA were identified in 1 proband and in *MYBPC3* in 2 probands.

Molecular Diagnosis of Syndromic Disease

Among the 242 probands with a MolDx of HCM, 86 (36%) were found to harbor a variant in a gene associated with a syndromic presentation. Most of the syndromic findings were in Rasopathy-associated genes (70%, 60/86) and 30% (26/86) were in genes associated with non-Rasopathy syndromes. Review of clinical information provided by ordering clinicians showed that 44% (38/86) of the probands with a syndromic MolDx of HCM had no reported clinical suspicion of syndromic disease at the time of testing. Figure 1

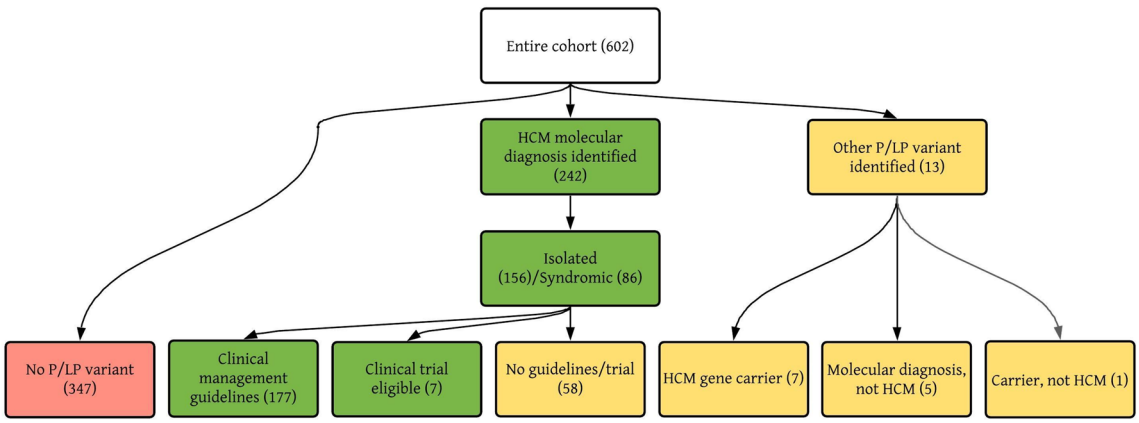

Fig. 1 Flowchart of the entire cohort. Of the entire cohort, 40% had a molecular diagnosis of HCM. Of these, 76% had disease-specific clinical management guidelines or conferred clinical trial eligibility. In green are the groups for whom genetic testing could impact clinical management of HCM; yellow indicates the groups which may have care of non-HCM disease or future considerations impacted by genetic testing; red demonstrates the patients for whom no pathogenic or likely pathogenic variant was identified. Parenthetical numbers indicate the number of patients in each group. *P/LP* pathogenic/likely pathogenic. *HCM* hypertrophic cardiomyopathy

Table 2 Precision medicine implications of molecular findings in HCM cohort

Gene	Management recommendations/trial eligibility[a,b]	Source
ACADVL	- Extracardiac disease monitoring/management, pregnancy considerations - Pharmacologic and dietary considerations Clinical trial eligibility: NCT03773770	PMID: 20301763
ACTC1	- Non-HCM cardiac disease monitoring/management	PMID: 28912181
AGL	- Pharmacologic and dietary considerations - Extracardiac disease monitoring/management	PMID: 20631546
BRAF	- Extracardiac disease monitoring/management	PMID: 23312968
	- Non-HCM cardiac and extracardiac disease monitoring/management	PMID: 25180280
CACNA1C	- Non-HCM cardiac and extracardiac disease monitoring/management - Pharmacologic, dietary, and surgical considerations	PMID: 20301577
CAPN3	- Extracardiac disease monitoring/management - Occupational therapy	PMID: 25313375
CBS	- Non-HCM cardiac and extracardiac disease monitoring/management - Dietary considerations	PMID: 27778219
CPT2	- Dietary and pharmacologic considerations	PMID: 20301431
DES	- Non-HCM cardiac disease monitoring/management	PMID: 28190577
	- Non-HCM cardiac and extracardiac disease monitoring/management	PMID: 31078652
FHL1	- Extracardiac disease monitoring/management	PMID: 29633897
	- Extracardiac disease monitoring/management - Pharmacologic considerations	PMID: 20301609
FKTN	- Extracardiac disease monitoring/management - Pharmacologic considerations	PMID: 25825463
FLNC	- Non-HCM cardiac disease monitoring/management	PMID: 31078652
GAA	- Non-HCM cardiac and extracardiac disease monitoring/management Clinical trial eligibility: NCT02354651, NCT01410890, NCT03911505, NCT04049760	PMID: 16702877
HRAS	- Non-HCM cardiac and extracardiac disease monitoring/management	PMID: 31222966
KRAS	- Non-HCM cardiac and extracardiac disease monitoring/management	PMID: 25180280
	- Non-HCM cardiac and extracardiac disease monitoring/management	PMID: 23312968
KCNQ1	- Non-HCM cardiac disease monitoring/management	PMID: 20301308
LAMP2	- Non-HCM cardiac disease monitoring/management Clinical trial eligibility: NCT03882437	PMID: 25228319
	- Extracardiac disease monitoring/management	PMID: 25228319
MYBPC3	- Non-HCM cardiac disease monitoring/management	PMID: 28912181
MYH7	- Non-HCM cardiac disease monitoring/management	PMID: 28912181
MYL2	- Non-HCM cardiac disease monitoring/management	PMID: 28912181
MYL3	- Non-HCM cardiac disease monitoring/management	PMID: 28912181
NF1	- Non-HCM cardiac and extracardiac disease monitoring/management	PMID: 31010905
PKP2	- Non-HCM cardiac disease monitoring/management	PMID: 3107852
PRKAG2	- Non-HCM cardiac and extracardiac disease monitoring/management	PMID: 26729852
PTPN11	- Extracardiac disease monitoring/management	PMID: 23312968
RAF1	- Extracardiac disease monitoring/management	PMID: 23312968
RIT1	- Extracardiac disease monitoring/management	PMID: 23312968
RYR1	- Extracardiac disease monitoring/management - Pharmacologic, surgical, and environmental considerations	PMID: 29600483; PMID: 26238698
SOS1	- Extracardiac disease monitoring/management	PMID: 23312968
TNNC1	- Non-HCM cardiac disease monitoring/management	PMID: 28912181
TNNI3	- Non-HCM cardiac disease monitoring/management	PMID: 28912181
TNNT2	- Non-HCM cardiac disease monitoring/management	PMID: 28912181
TPM1	- Non-HCM cardiac disease monitoring/management	PMID: 28912181
TTR	- Extracardiac disease monitoring/management	PMID: 20301373

[a]Based on gene or clinical diagnosis-specific guidelines. Broad recommendations, such as those included in cardiogenetics guidelines addressing the genetic evaluation of HCM or cardiomyopathies, are not included

[b]Search conducted on 5/13/2020 in clinicaltrials.gov using the following parameters: interventional, < 18 years of age, gene name or genetic diagnosis used as part of recruitment, and status = recruiting

provides a summary of the overall breakdown of the above-described groups.

Age at Testing and Gene Type

A MolDx of syndromic HCM was associated with a much earlier age at testing with a median age at testing of syndromic HCM of 4 years vs. median age at testing of isolated HCM of 12 years ($p < 0.001$) (Fig. 2). Individuals with a Rasopathy MolDx contributed significantly to the earlier age at testing (median age at testing of Rasopathy MolDx of 1 year vs. median age at testing of non-Rasopathy MolDx of 13.5 years, $p < 0.001$).

Family Variant Testing

Cascade testing of 434 family members was carried out in the families of 129 unrelated probands. On average, 3.4 family members were tested per proband (range 1–46). Of the 434 family members tested, 178 (41.0%) were identified as carrying ≥ 1 HCM disease-causing variant. Family variant testing was accomplished in at least one at-risk relative for 121/242 (50%) probands with a MolDx of HCM.

Discussion

This study is novel in determining how often a MolDx goes beyond providing just a diagnosis to impacting clinical management in HCM among pediatric patients. A MolDx was determined in 40 percent of patients, which is comparable to previously published rates [2, 5]. However, we observed significant disparities in MolDx yield by race/ethnicity, with a significantly reduced ability to provide a MolDx for Black probands. Additionally, we show that among all probands who received a MolDx, three-quarters had P/LP variants in genes with established management recommendations and/or gene-specific clinical trial eligibility. Precision medicine remains a developing field and some of the available guidelines inform the management of categories of variants, as opposed to being gene specific. For example, the diagnostic variants in the sarcomeric genes *MYH7* and *TNNT2* have the same management recommendations. As precision medicine progresses, it is possible recommendations will become increasingly variant specific. As this body of knowledge is nascent, guidelines continue to be developed and ultimately will need large-scale validation.

This study is also novel in showing that 38 of the 86 (44%) patients in this cohort with a MolDx of a syndromic form of HCM were not reported by ordering clinicians to

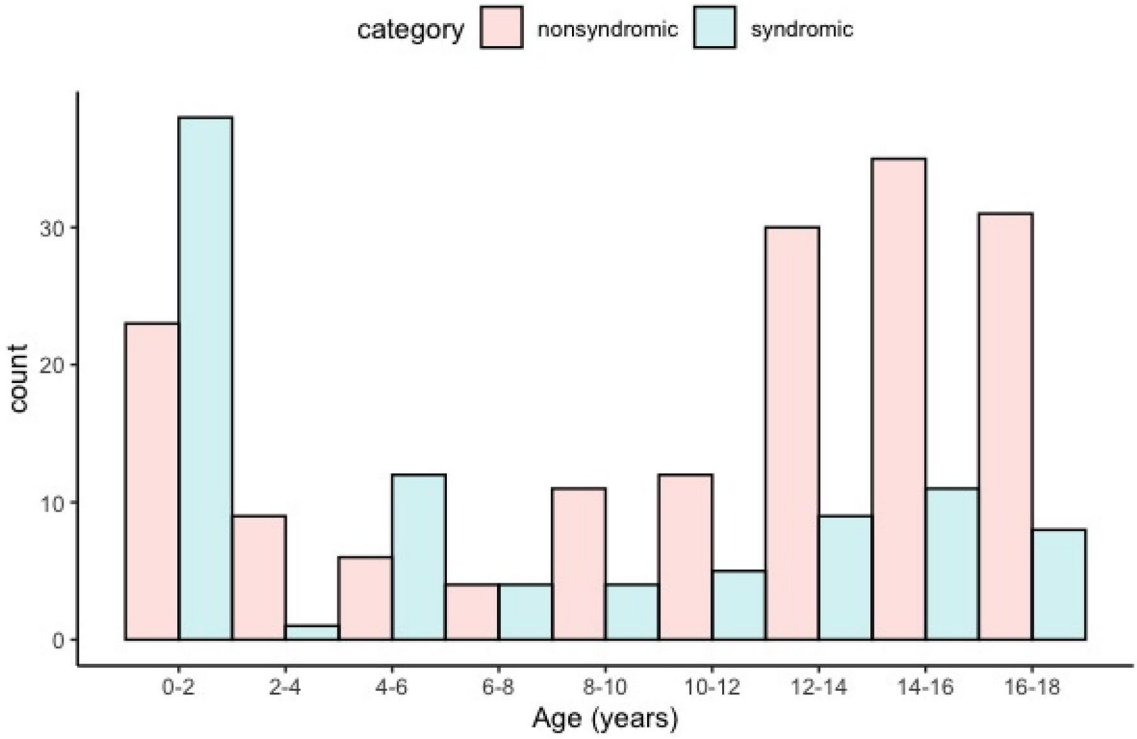

Fig. 2 Plot demonstrating count of syndromic versus non-syndromic cases of HCM stratified by age at testing. Syndromic HCM was associated with an earlier age when compared with non-syndromic HCM, although both types of cases were diagnosed across the entire age range

have clinical evidence of a genetic syndrome at the time of genetic testing. The 2011 ACCF/AHA guideline for HCM distinguishes between isolated HCM (patients with sarcomeric variants/without extracardiac findings and unresolved genetic substrate) and patients with left ventricular hypertrophy as part of a syndrome, including extracardiac findings or metabolic disease [10]. This distinction is upheld in the updated 2020 AHA/ACC guideline which refers to patients with systemic disorders and left ventricular hypertrophy as "HCM Phenocopies" [7]. However, distinguishing between these patients based on phenotype alone is often difficult, particularly early in life when subtle facial dysmorphisms or other extracardiac manifestations may not be apparent and HCM may be the only evident manifestation of a genetic syndrome. By showing that 38 patients in whom clinical evidence of a syndrome was not reported in fact had P/LP variants in genes associated with a syndromic form of HCM, our results help define and quantify the number of patients who would have been missed or misdiagnosed without comprehensive multigene panel genetic testing. Prior reports with smaller cohorts have reported syndromic variants among patients with seemingly isolated HCM, although at lower rates than in our cohort [11]. One factor potentially leading to a large number of patients with syndromic diagnoses being missed is the strategy of ordering the narrowest panel of gene tests based on a clinician's hypothesis of likely genetic etiology from patient phenotypes [12, 13]. This approach of limiting the number of genes included on the panel likely results in missed identification of syndromic patients who would otherwise have benefitted from earlier intervention and gene-based precision clinical management had their syndrome been diagnosed genetically earlier in life [10, 13]. The inverse is likely also true that testing too narrowly for a suspected syndromic mutation based on phenotype may result in missed or delayed diagnosis of other syndromes or non-syndromic disease.

We also found that nearly half of proband relatives who underwent cascade family variant testing were found to have HCM disease-causing variants. The role of genetic testing in screening for disease susceptibility among asymptomatic family members has been central to the discussion of the clinical utility of genetic testing [7, 14]. While not impacting the clinical management of the probands, identification of affected or at-risk family members do allow for appropriate screening for clinical disease or, for those with negative testing, relief from unnecessary cardiac surveillance testing and anxiety over risk for disease. Effective cascade family variant testing also supports efficient health care resource utilization by helping to focus cardiac surveillance on family members with confirmed genetic risk. As precision medicine continues to develop, cascade testing lends support to genetic testing of probands as a form of changing clinical management.

In this cohort, it is notable that a MolDx was least frequently achieved for Black patients despite epidemiologic data showing that HCM occurs at similar rates among Black populations compared to other races and ethnicities, with some reports suggesting HCM may be more common in this group [15–17]. This lower rate of achieving a MolDx for Black patients has also been described among adult HCM cohorts [18]. There are several potential reasons for this lower yield, many of which are confounded by challenges with access to genetic testing among non-White populations. Indeed, the 2020 AHA/ACC guideline does note that the non-White HCM population has fewer described high-quality genetic data [7]. It is possible that novel variants found in Black populations have not been studied enough to allow them to be classified as anything except variants of unknown significance, as has been the case for other diseases [19]. Lack of knowledge of variants in non-White population also introduces the risk for misclassification of benign variants as pathogenic [20]. It is also possible that a greater proportion of the genes involved in HCM in Black patients are still unknown and untested. There may also be environmental, non-genetic factors that can contribute to the development of HCM which affect Black children disproportionately. Finally, the pre-test probability for a MolDx of HCM in Black patients may be lower because of the contribution of racial bias in the actual definition of HCM. Black patients were underrepresented in the development of Z-scores so it possible that non-pathologic LVH among Black patients could be misclassified as HCM, reducing the likelihood that a MolDx would be identified [20].

While investigating the reason for this disparity was beyond the scope of this study, the differential ability to provide a MolDx for Black HCM patients likely confers a reduced ability to provide targeted clinical management for these patients, potentially contributing to racial health inequities. A known impact of the relative paucity of sequencing data in underrepresented populations is the risk for misclassification of benign variants as disease causing [21]. There are known systemic and individual-level barriers to genetic testing among Black patients ranging from baseline knowledge and apprehensions about testing related to historical injustices to differences in coverage for genetic testing between public and private insurances [22, 23]. These issues must be addressed. Improved understanding and increased access to genetic testing for HCM in Black patients are needed to ultimately offer the same benefits from MolDx provided to individuals of other races or ethnicities.

While we focused specifically on HCM, it is reasonable to theorize that our findings relate to other diseases that have historically relied upon phenotypic or clinical and diagnosis. Through genetic testing, we can now confirm or refute these clinical diagnoses. Indeed, we now understand patients with the same phenotype may have different underlying

mutations warranting different management strategies [24]. Conversely, patients with different phenotypic presentations may share the same genetic substrate [11, 25]. Our findings highlight the importance of broad, unbiased genetic testing and demonstrate how genetic testing results can help patients and their families. Knowledge that a MolDx can impact clinical management, including acute treatment, may influence general practitioners, who may be less comfortable utilizing genetic testing, to pursue it more frequently [26, 27]. Unfortunately, our findings also recapitulate that diminished access to precision medicine due to inadequate genetic understanding of Black patients may exacerbate ongoing, multifactorial health inequities.

This study has several limitations, including its retrospective design and the inability to access full clinical data for patients. In particular, we were unable to definitively determine if patients with syndromic mutations had extracardiac disease. Although the reported clinical data submitted with testing orders indicated suspicion of syndromic disease in some cases, we cannot be certain of the details regarding why syndromes were or were not suspected. Similarly, we did not have sufficient clinical data to evaluate the correlation between phenotypes and MolDx. Additionally, it is possible that some negative results were a reflection of providers ordering smaller panels that did not analyze the gene(s) relevant to their patient's condition. We also cannot report whether the clinical management recommendations based on MolDx were implemented or whether patients eligible for clinical trials were actually enrolled. Additionally, as genetic testing has proliferated in the clinical setting, concerns have been raised regarding the emotional impact on families awaiting results, confidentiality of results, and results that include secondary findings or variants of unknown significance [28]. Other fears such as impact on insurability are also common among families [28]. As with any intervention in medicine, these concerns and risks must be weighed against potential benefit and, fortunately, many may be mitigated with genetic counseling and other best practices both prior to testing and after receiving results of testing [29, 30].

Conclusion

Almost half of our cohort of patients with clinically diagnosed HCM received a MolDx, a substantial portion of which were syndromic. The majority of patients with a MolDx of HCM had P/LP variants in genes with established management recommendations and/or gene-specific clinical treatment trial eligibility. Some of the currently available management recommendations, particularly for non-syndromic HCM, are for categories of variants rather than being gene specific. The diagnostic yield in Black patients with HCM was significantly less than that of other populations, underscoring the need for genetic research in this historically understudied population and suggesting additional genetic etiologies of HCM have yet to be elucidated. These data reinforce the importance of comprehensive multigene panel genetic testing to facilitate an accurate and early diagnosis and demonstrate the clinical utility of genetic testing in treatment planning. This may be relevant for other diseases of genetic etiology which have traditionally been diagnosed based on clinical or phenotypic findings.

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Data Availability Not applicable.

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Declarations

Conflict of interest AM, TC, JG, SR, RT, MV, RLN, and EDE are employees and stockholders of Invitae. JRP is an employee and stockholder of BioMarin Pharmaceutical which has publicly disclosed early-stage therapeutic approaches to HCM. All other authors have indicated that they have no potential conflict of interest to disclose.

Ethical Approval This study was approved by the Western Independent Review Board, protocol number 1167406.

Consent to Participate Not applicable.

Consent for Publication All authors are responsible for reported research and have approved the manuscript as submitted.

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