



ORIGINAL RESEARCH

Establishment of a Dedicated Inherited Cardiomyopathy Clinic: From Challenges to Improved Patients' Outcome

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BACKGROUND: Inherited cardiomyopathies (ICs) are relatively rare. General cardiologists have little experience in diagnosing and managing these conditions. International societies have recognized the need for dedicated IC clinics. However, only few reports on such clinics are available.

METHODS AND RESULTS: Clinical data of patients referred to our clinic during its first 2 years for a personal or family history of (possible) IC were analyzed. A total of 207 patients from 196 families were seen; 13% of probands had their diagnosis changed. Diagnosis was most commonly altered in patients referred for possible arrhythmogenic dominant right ventricular cardiomyopathy (62.5%). A total of 90% of probands had genetic testing, of whom 27.3% harbored a likely pathogenic or pathogenic variant. Of patients with confirmed hypertrophic cardiomyopathy, 31 (28.7%) were treated for left ventricular outflow tract obstruction, including septal reduction in 13. Patients with either hypertrophic cardiomyopathy or left ventricular noncompaction and a history of atrial fibrillation were started on oral anticoagulation. Oral anticoagulation was also discussed with all patients with hypertrophic cardiomyopathy and apical aneurysm. Patients with a definite diagnosis of arrhythmogenic dominant right ventricular cardiomyopathy were started on β -blockers and given restrictive exercise prescriptions. A total of 17 patients with hypertrophic cardiomyopathy and 5 patients with likely pathogenic or likely variants in arrhythmogenic genes received primary prevention implantable cardioverter-defibrillators. No implantable cardioverter-defibrillators were warranted for arrhythmogenic dominant right ventricular cardiomyopathy. A total of 76 family members from 24 families had cascade screening, 32 of whom carried the familial variant. A total of 21 members from 13 gene-elusive families were evaluated by clinical screening, 3 of whom had positive screening.

CONCLUSIONS: Specialized IC clinics may improve diagnosis, management, and outcomes of patients with (possible) IC and their family members.

Key Words: genetics ■ implantable cardioverter-defibrillators ■ inherited cardiomyopathy

Inherited cardiomyopathies (ICs) include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), left ventricular noncompaction (LVNC), restrictive cardiomyopathy, and 3 types of arrhythmogenic cardiomyopathy, including arrhythmogenic dominant right ventricular cardiomyopathy (ARVC), arrhythmogenic dominant left ventricular cardiomyopathy, and arrhythmogenic cardiomyopathy with biventricular involvement.¹ Genetic testing and advanced imaging

have shown that the prevalence of IC is higher than previously thought (eg, HCM prevalence of 1:200–300 versus 1:500).^{2–4} Yet, ICs are still relatively rare and general cardiologists have little experience in diagnosing and managing individuals with these conditions and screening their family members. Consequently, experts and international societies, such as the American Heart Association, have recognized the need for dedicated clinics for IC.⁵ There are few reports on the

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CLINICAL PERSPECTIVE

What Is New?

- Specialized inherited cardiomyopathy (IC) clinics can improve diagnosis, management, and outcomes of patients with IC and their family members.

What Are the Clinical Implications?

- There is a need for dedicated clinics for IC with appropriate personnel and expertise.
- Efforts should be made through continuing education for cardiologists to learn how to identify individuals and families who may benefit from referral to a dedicated IC clinic.
- All patients with a personal or family history of (possible) IC should be referred to a dedicated IC clinic.

Nonstandard Abbreviations and Acronyms

ARVC	arrhythmogenic dominant right ventricular cardiomyopathy
DCM	dilated cardiomyopathy
FHSCD	family history of sudden cardiac death
FLNC	filamin C
HCM	hypertrophic cardiomyopathy
HVI	Heart and Vascular Institute
IC	inherited cardiomyopathy
LMNA	lamin A/C
LP/P	likely pathogenic or pathogenic
LVNC	left ventricular noncompaction
LVOTO	left ventricular outflow tract obstruction
MYBPC3	myosin-binding protein C3
MYH7	myosin heavy chain 7
OAC	oral anticoagulation
PKP2	plakophilin 2
RBM20	RNA-binding motif protein 20
TTE	transthoracic echocardiogram
VUS	variant of uncertain significance

establishment of such clinics and their impact on patients' outcomes.⁶⁻⁸ Therefore, we sought to describe our experience in establishing a dedicated IC clinic and its benefits to patients and their family members.

METHODS

The authors declare that all supporting data are available within the article. Further details of the analyses of the study are available from the corresponding author on request.

Development of the Program

As one of the largest tertiary cardiac and teaching centers in New England, the Heart and Vascular Institute (HVI) medical leadership recognized the clear need for a specialized program for IC as part of their vision of providing a full array of services for the residents of the state and neighboring areas. Before the program launch, there was only one program for IC in the state of Connecticut. The existing program provided access to a few regions in Connecticut, and patients from other regions were referred to out-of-state centers (mostly to Boston, MA).

The business/administrative stakeholders were focused on understanding the associated revenue streams and on assessing the potential profitability of such a service line. Before the program launch, HVI finance team developed a business plan. It is crucial for the plan to project the program's financial success not only based on direct revenues from consult and follow-up visits of patients and their families but also on the substantial downstream revenue that such a program would generate from advanced imaging, device implantations, and invasive procedures. On the basis of the prevalence of the in-scope conditions, the number of the potential patients in the geographical area can be estimated. Extrapolating the associated downstream activities (eg, septal myectomy and implantable cardioverter-defibrillator [ICD]) based on available reference data, finance teams were able to deem such a program as economically viable. Finance teams often focus on direct revenues only if not provided with disease prevalence estimates and the percentage of patients who will require downstream evaluations and management. This limits the perspective required to determine that such a program is economically viable. Hence, dialog between the medical and financial stakeholder was a key success factor. Also, as ICs have been shown to be underdiagnosed, the business plan considered an increase in local awareness among the local cardiologists and primary care physicians by the program, resulting in a gradual increase in referral. This was expected to have an effect beyond providing the existing market with a local alternative (share of wallet) and to generate "net new" revenues from patients who would have otherwise remained undiagnosed. The first step in building the program was recruiting a cardiologist with specialized training and experience in cardiovascular genetics as the director of the program. In parallel, a cardiothoracic surgeon trained at septal myectomy was also recruited. Once hired, the director also worked across HVI services to identify clinicians who would be members of the multidisciplinary team, such as those who work in advanced heart failure, cardiothoracic surgery, electrophysiology, interventional cardiology, and cardiac imaging. When an identifiable

resource was not available, HVI administration worked with the program director to recruit these clinicians or provide the required training and proctoring to existing resources. One such example is a genetic counselor with experience in cardiovascular genetics who was recruited to focus only on the program. To continue to grow the program, HVI promoted the program in local media and arranged meet and greets for the program director with cardiologist groups across Connecticut to introduce and highlight the program and increase awareness to ICs. The program director gave grand rounds for cardiologists and other medicine specialists in hospitals across Connecticut. The program director and genetic counselor also gave talks and webinars to patients. A website dedicated to the program was developed by the HVI.

Population

The data of patients referred to the clinic were routinely entered into a database and retrospectively analyzed. Patients were referred to the clinic for suspected ICs, including HCM, DCM, ARVC, LVNC, family history of cardiomyopathy, or family history of sudden cardiac death (FHSCD) suspected to be attributable to non-ischemic cardiomyopathy. Individuals with an FHSCD attributable to a primary electrical disorder or without an autopsy were not included in this report. Only patients aged ≥ 18 years were seen in the clinic.

Diagnostic Workup

The diagnostic workup varied by the suspected condition, although all patients met with a certified genetic counselor who took a detailed family history to construct a 4-generation pedigree. Patients underwent a transthoracic echocardiogram (TTE), cardiac magnetic resonance (CMR) (if no contraindication was present), and ambulatory ECG monitoring via a Holter monitor or event recorder. Patients with HCM and without left ventricular outflow tract obstruction (LVOTO) (gradient, < 30 mm Hg at rest or with the Valsalva maneuver) underwent a stress TTE to assess for latent obstruction. Most patients with obstructive HCM (ie, gradient ≥ 30 mm Hg), including those with no or mild symptoms, also underwent stress TTE to assess their exercise capacity. Transesophageal echocardiography was also performed in selected cases to assess the mitral valve anatomy and regurgitation. Most patients with DCM or HCM underwent a cardiopulmonary exercise stress test. Patients with suspected ARVC also underwent an exercise treadmill test and signal average ECG, and in specific cases, pharmacological testing with isoproterenol to differentiate ARVC from idiopathic right ventricular outflow tract ventricular tachycardia.⁹ Imaging studies were repeated after 3 to 6 months of

detraining in selected instances when the patient presentation was most consistent with an athlete's heart. A stress TTE was also performed to help differentiate athlete's heart from possible mild DCM.¹⁰ An electrophysiology study was performed and/or an insertable cardiac monitor was placed in selected cases.

Patients with a FHSCD were tested according to the diagnosis of the deceased family member and autopsy findings. The coroner and/or pathologist were contacted to obtain available genetic material if a molecular autopsy had not been performed.

Genetic Testing

Genetic testing for a proband was done using commercially available broad pan cardiomyopathy and arrhythmia panels. These panels are College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments certified and use next-generation sequencing and hybridization with deletion and duplication analysis. Variants were classified using the American College of Medical Genetics and Genomics guidelines.¹¹ The genetic cardiologist and genetic counselor interpreted the genetic tests using available data from ClinVar, ClinGen, PubMed, and other sources. In certain cases when a variant of uncertain significance (VUS) was identified, we contacted different genetic laboratories that had previously reported the variant.

The type of specimen available from the autopsy determined the genetic testing for molecular autopsy. We used the commercial Clinical Laboratory Improvement Amendments- and CAP-approved panel mentioned above if blood was available and used exome sequencing, which also was CAP and Clinical Laboratory Improvement Amendments approved, through a commercial academic laboratory if only tissue was available.

Family members were evaluated by follow-up pathways depending on the genetic testing results. First-degree relatives of families with a likely pathogenic or pathogenic (LP/P) variant were offered single-site genetic testing first. Genetically positive family members and those choosing not to undergo genetic testing were recommended to undergo clinical screening. Family members who were genetically negative for the LP/P variant were not referred for additional testing. A first-degree family member whose genetic testing was negative or in whom a VUS was identified was referred for clinical screening based on current guidelines.¹²⁻¹⁴ Phenotypically positive members of families with a VUS favoring LP variant were offered single-site genetic testing. The recommended pathway for genetic testing or clinical screening was outlined for family members via a letter from the genetic counselor after the proband had been genetically tested.

Statistical Analysis

Continuous variables are presented as mean (SD), and qualitative variables are expressed as count (percentage).

This study was approved by the Hartford Healthcare/Hartford Hospital institutional research board (HHC-2021-0324). Informed consent was waived.

RESULTS

Patients

We evaluated 207 patients from 196 families during the clinic's first 2 years (March 1, 2019, to March 31, 2021) for either a personal or family history of definite or possible IC (Table 1). Referrals increased progressively, except for the peak of the COVID-19 pandemic (February to May 2020), as depicted in Figure 1. HCM accounted for 59.4% of referrals; 87.9% of patients were probands (Table 1).

Two or more years had elapsed since initial diagnosis to clinic referral in 44% of probands referred for HCM and 62% of probands referred for DCM. These patients could not recall or had not been given genetic counseling or recommendations for family screening.

Diagnosis Changed

Of probands, 13% had their diagnosis changed by our clinic. The diagnosis was changed in 62.5% of probands evaluated for (possible) ARVC (Table S1). The most common cause for overdiagnosis of ARVC was incorrect interpretation of the CMR. In about 13% of probands referred for (possible) HCM, the diagnosis was most commonly changed to hypertensive cardiomyopathy, athlete's heart, or sigmoid septum of the elderly. In 2 cases, the diagnosis was changed to wild-type transthyretin cardiac amyloidosis; and in 1 case, the diagnosis was changed to cardiac sarcoidosis. In 1 patient with genotype-positive HCM, a diagnosis of congenital long QT 2 syndrome was added. In 1 of 3 patients referred for isolated LVNC, the diagnosis was changed after reviewing the CMR and TTE, which did

not meet the diagnostic criteria for LVNC. In 3 patients referred for a personal history of DCM, the diagnosis was changed to athlete's heart.

Patients With Family History of Cardiomyopathy-Related Sudden Cardiac Death

Nine patients from 7 families were evaluated for cardiomyopathy attributable to cardiomyopathy-related FHSCD based on autopsy findings. We were able to arrange molecular autopsies in 3 of these families. The molecular autopsy in a family whose proband died of DCM detected an LP variant in the filamin C (*FLNC*) gene (c.5199+1G>T). The proband's mother and brother tested positive for the *FLNC* variant and had mild left ventricular dysfunction on CMR. There were 2 additional sudden cardiac deaths in the family. The first was the proband's 20-year-old sister, whose death was attributed to "idiopathic ventricular fibrillation" after her autopsy showed a structurally normal heart. The second was the proband's 29-year-old maternal uncle, whose autopsy showed DCM and is an obligatory carrier. An ICD for primary prevention was implanted in both the proband's brother and mother, and cascade screening was performed for the extended family (Figure 2).

The second family's proband's autopsy showed DCM. The molecular autopsy identified an LP variant in plakophilin 2 (*PKP2*) (c. 1489C>T). The autopsy slides did not demonstrate evidence of ARVC on review. The association of *PKP2* variants with DCM is controversial, leaving it unclear if this variant caused this family's DCM and sudden cardiac death. The decedent's brother and niece have subsequently been diagnosed with DCM and are being evaluated to determine the role of the variant in *PKP2* in the familial DCM.

The third family's proband's autopsy showed biventricular dilatation and hypertrophy with multifocal left ventricular myocardial fibrosis and fibrosis of the His bundle. The molecular autopsy did not identify variants in genes associated with cardiomyopathy. The family is undergoing clinical screening.

Table 1. Patients' Characteristics by Referral Diagnosis Conditions

Condition	No.	Proband, n (%)	Age, mean (SD), y	Male sex, n (%)	Diagnosis changed in probands, n (%)
All cohort	207	183 (87.9)	49 (16)	131 (62.9)	24 (13.1)
HCM	123	114 (92.7)	51 (16)	78 (63.4)	15 (13.2)
DCM	62	58 (93.5)	48 (14)	40 (63.4)	3 (4.8)
ARVC	10	8 (80.0)	45 (19)	8 (80.0)	5 (62.5)
iLVNC	3	3 (100)	47 (8)	1 (33.3)	1 (33.3)
Cardiomyopathy-related FHSCD	9	0 (0)	35 (11)	4 (44.4)	0 (0)

ARVC indicates arrhythmogenic dominant right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; FHSCD, family history of sudden cardiac death; HCM, hypertrophic cardiomyopathy; and iLVNC, isolated left ventricular noncompaction.

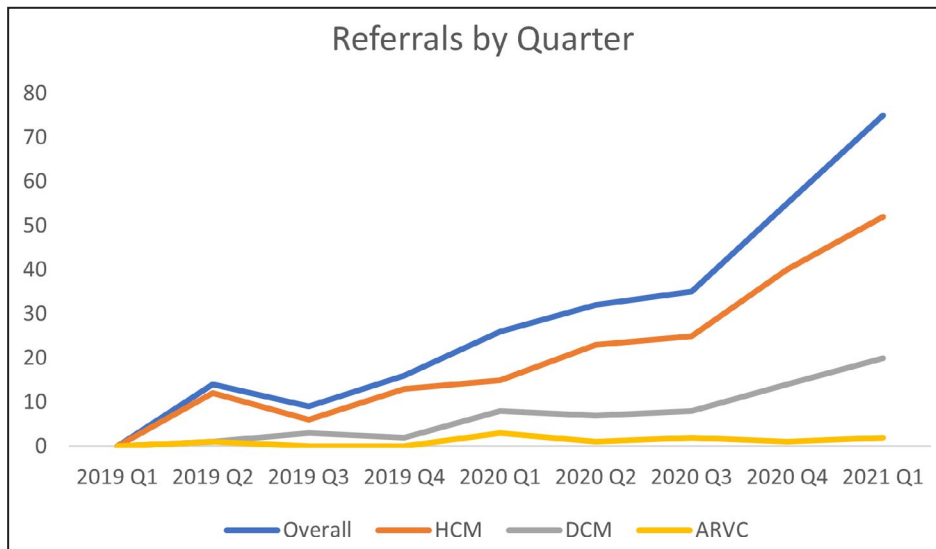


Figure 1. Growth of program by quarter (Q).
ARVC indicates arrhythmogenic dominant right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; and HCM, hypertrophic cardiomyopathy.

Molecular autopsy was not available for 4 families. The remaining 5 family members of these families underwent clinical screening and genetic testing for ARVC (2 families), HCM (1 family), and DCM (1 family). Screening was positive in 2 family members who underwent a primary ICD implantation (Table S2).

time, genetic counseling was performed by the genetic cardiologist. Of probands, 90% (165/183) had genetic testing. Eighteen probands declined genetic testing for a variety of reasons, including logistics, COVID-19 concerns, or absence of younger family members. An LP/P variant was identified in 27.3% of the 165 probands who underwent genetic testing (Table 2). Genes and frequency of LP/P variants identified for HCM and DCM are summarized in Tables 3 and 4, respectively. *MYBPC3* (myosin binding protein C3) was most common gene in HCM (55.2%) (Table 3). *TTN* (titin), *FLNC*,

Genetic Testing

Recruitment of a qualified genetic counselor lasted over a year because of the small applicant pool. During this

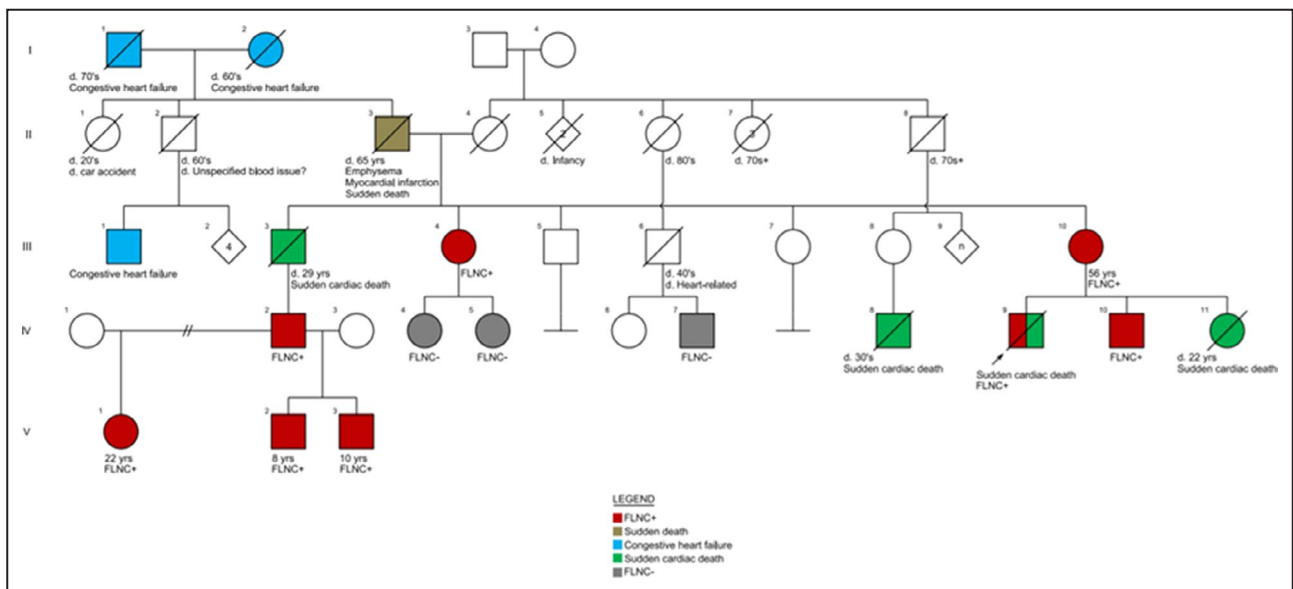


Figure 2. Cascade screening a family with sudden cardiac death caused by a likely pathogenic variant in filamin C gene (FLNC).

Table 2. Yield of Genetic Testing in Probands by Initial Diagnosis

Condition (n)	Probands undergoing genetic testing, n (%)	LP/P variant (% of those tested)	VUS (% of those tested)
All probands (183)	165 (90.2)	46 (27.3)	49 (30.3)
HCM (114)	99 (86.8)	29 (29.3)	22 (22.2)
DCM (58)	55 (94.8)	13 (23.6)	23 (41.8)
ARVC (8)	8 (100)	2 (25.0)	2 (25.0)
iLVNC (3)	3 (100)	1 (33.3)	1 (33.3)
FHSCD (0)	3 (33.3)*	2 (66.7)	1 (33.3)

ARVC indicates arrhythmogenic dominant right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; FHSCD, family history of sudden cardiac death; HCM, hypertrophic cardiomyopathy; iLVNC, isolated left ventricular noncompaction; LP/P, likely pathogenic or pathogenic; and VUS, variant of uncertain significance.

*Molecular autopsy.

and *RBM20* (RNA-binding motif protein 20) were the most common genes identified in DCM (Table 4), and *PKP2* gene in ARVC. Tables S3 and S4 list variants and their classification by condition.

Change in Management

Of patients with confirmed HCM, 31 were treated for LVOTO by discontinuation of vasodilators (n=7), initiation or up titration of β -blockers, or addition of nondihydropyridines calcium channel blockers (n=20), initiation of disopyramide (n=17), and surgical (n=12) or alcohol (n=1) septal reduction. All patients with confirmed HCM and atrial fibrillation (AF) or flutter were started on oral anticoagulation (OAC). Three patients underwent AF catheter ablation. All patients with a history of AF who underwent surgical septal myectomy had a concomitant MAZE procedure, and 3 of these patients also underwent a left atrial appendage closure. OAC was also discussed with the 3 patients with an apical aneurysm and no diagnosis of AF or other indications for anticoagulation.¹⁵

All patients with a definite diagnosis of ARVC were started on β -blockers and were given a restrictive exercise prescription.¹⁶ Similar exercise prescriptions were given to phenotype-negative gene carriers.¹⁶ One of the 2 patients with confirmed isolated LVNC had AF and was started on OAC despite a $\text{CHA}_2\text{DS}_2\text{-VASc}$ (Congestive heart failure, Hypertension, Age (>65=1 point, >75=2 points), Diabetes, previous Stroke/transient ischemic

attack (2 points), vascular disease, and sex category (female gender)) score of 0 attributable to the increased risk of thromboembolism with AF in LVNC.¹³ All patients were offered a referral to a health psychologist.

Implantable Cardioverter-Defibrillators

Seventeen of 114 patients with HCM and no ICDs underwent a primary prevention ICD implantation (transvenous [n=13], subcutaneous [n=3], and biventricular [n=1]). No ICDs were warranted in any patients with ARVC. In 2 of the 5 patients whose initial diagnosis of ARVC was altered by our clinic, a primary prevention ICD for ARVC had been previously recommended. Furthermore, one of them had undergone a primary prevention ICD implantation that was complicated by pocket infection and *Staphylococcus aureus* bacteremia requiring lead extraction. This patient was wearing a LifeVest when first seen in our clinic. In 3 cases of DCM, genetic testing detected LP/P variants in arrhythmogenic genes and hence we proceeded with a primary prevention ICD implantation (*LMNA* (lamin A/C) and *FLNC*) and a dual-chamber pacemaker upgrade for biventricular ICD despite normal left ventricular function (*desmin*) (Table S5).

Family Screening

Forty-six probands, including 2 with molecular autopsies, had a positive genetic result. A total of 76 family members from 24 families had single-site genetic testing because of a known familial LP/P variant. The average number per family was 3 members (range, 1–11). Thirty-two of these family members were found to carry the familial variant.

For those with negative genetic testing, those with a VUS, or those who were unwilling to have genetic testing, we recommended clinical screening of their family members. Twenty-one members of 13 gene-elusive families were evaluated by clinical screening. The average number of members per family was 2 (range, 1–3). We identified an additional family member by clinical screening in 3 families. We have recently started using

Table 3. HCM Genes and Frequency of LP/P Variants

Gene	Frequency, n (%)
<i>MYBPC3</i>	16 (55.2)
<i>MYH7</i>	5 (17.2)
<i>TNNI3</i>	4 (13.8)
<i>ACTC1</i>	2 (6.9)
<i>GLA</i>	1 (3.4)
<i>PLN</i>	1 (3.4)

ACTC1 indicates actin α cardiac muscle 1; *GLA*, galactosidase α ; HCM, hypertrophic cardiomyopathy; LP/P, likely pathogenic or pathogenic; *MYBPC3*, myosin-binding protein C3; *MYH7*, myosin heavy chain 7; *PLN*, phospholamban; and *TNNI3*, troponin I3.

Table 4. DCM Genes and Frequency of LP/P Variants

Gene	Frequency, n (%)
<i>TTN</i>	3 (22.1)
<i>FLNC</i>	2 (15.4)
<i>RBM20</i>	2 (15.4)
<i>TTR</i>	2 (15.4)*
<i>BAG3</i>	1 (7.7)
<i>DES</i>	1 (7.7)
<i>DSG2</i>	1 (7.7)†
<i>DSP</i>	1 (7.7)†
<i>LMNA</i>	1 (7.7)

BAG3 indicates BAG co-chaperone 3; DCM, dilated cardiomyopathy; *DES*, desmin; *DSG2*, desmoglein 2; *FLNC*, filamin C; *LMNA*, lamin A/C; LP/P, likely pathogenic or pathogenic; *RBM20*, RNA-binding motif protein 20; *TTN*, titin; and *TTR*, transthyretin.

*One individual was homozygous for *TTR*, and another was heterozygous.

†The same person had both of these genes.

genome or exome sequencing for these gene-elusive families with multiple affected family members.

We tested other family members to help clarify the significance of a VUS when family members demonstrated the phenotype. For example, we used this method for a VUS in *MYH7* (myosin heavy chain 7) (c.121G>A) to determine that it was not the cause of the family’s DCM (Figure 3).

DISCUSSION

The need for dedicated IC clinics has been increasingly acknowledged. In 2019, the American Heart Association published a Scientific Statement on the need and requirements for clinical cardiovascular

genetic programs.⁵ Such programs still do not exist in most centers, and most patients with these inherited conditions are managed by cardiologists without special training in cardiac genetics. This report summarizes our experience in establishing an IC clinic to illustrate how such programs can benefit patients and their families.

A major obstacle to establishing such programs is health centers’ concern that IC clinics do not generate high revenue. Furthermore, genetic counselors in Connecticut and many other states cannot charge for their service. However, as demonstrated by our report, these programs bring patients and relatives into the health system, and these individuals require testing and procedures. Downstream revenue from imaging studies and procedures should be tracked to measure the financial viability of these programs as these are substantial and reflect the bulk of revenues generated by such programs.

Raising awareness of the program among potential referring physicians is another challenge as well as a growth opportunity. We provided educational sessions for physicians and the community, met with cardiology groups, and collaborated with the local children’s hospitals. These measures raised awareness and led to an exponential growth in referrals.

Referral for DCM broadened as the cardiologists became aware that genetic factors also predispose patients to develop DCM of a “known cause” (eg, alcoholic, myocarditis-related, and postpartum cardiomyopathies). In fact, when taking a detailed 3-generation family history, some individuals initially diagnosed with “idiopathic” or “sporadic” DCM were ultimately found to have family history of heart failure or sudden death. An

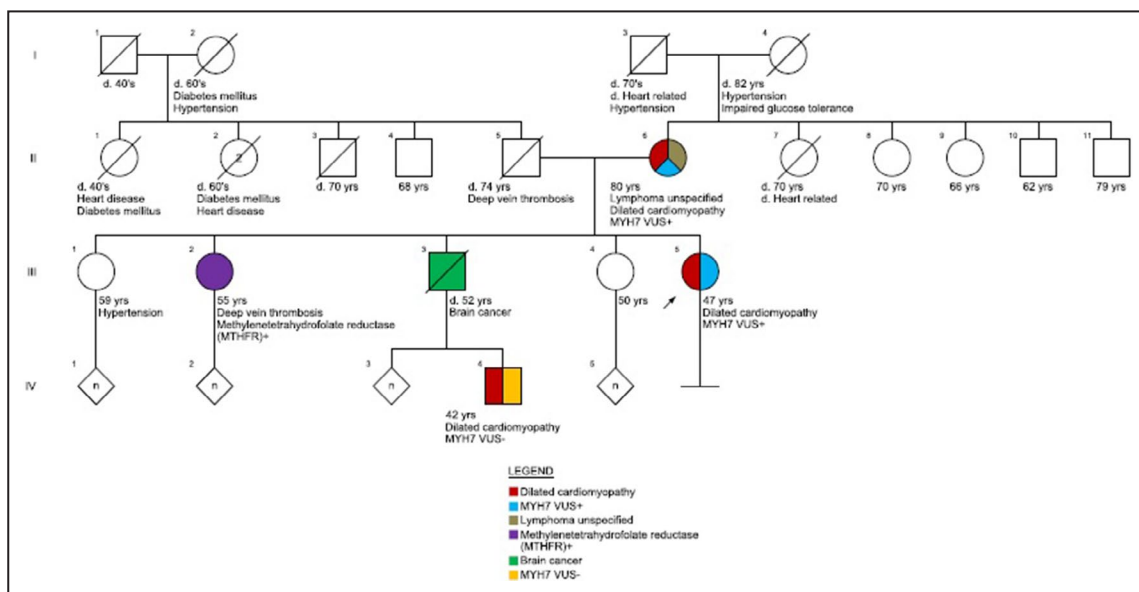


Figure 3. Variant of uncertain significance (VUS) in myosin heavy chain 7 (*MYH7*) resolution in a family with dilated cardiomyopathy.

LP/P variant was found in 1 of every 4 patients referred for DCM. Genetic testing in DCM also contributes to risk stratification when an LP/P variant is found in one of the arrhythmogenic genes (eg, *FLNC*, *SCNA5A*, *RBM20*, *LMNA*, or *desmin*). Indeed, the presence of an LP/P variant in the arrhythmogenic genes (ie, *FLNC*, *LMNA*, and *PLN*) has been incorporated into the recommendations for primary prevention ICD by the 2019 Heart Rhythm Society guidelines for arrhythmogenic cardiomyopathy.¹³ We recommend genetic testing for all patients with DCM. The yield of genetic testing for DCM in our clinic was $\approx 24\%$ for LP/P variants, which is consistent with other studies.^{17–19} We found LP/P variants in arrhythmogenic genes (ie, *LMNA*, *FLNC*, and *desmin*) in 3 probands with DCM and in the mother and brother of a proband referred for FHSCD (*FLNC*). All these individuals received a primary prevention ICD.

In line with previous reports, diagnoses were frequently changed.^{20,21} The diagnosis was most frequently changed primarily in patients referred for possible ARVC, where $>60\%$ had their diagnosis changed mainly because of overdiagnosis of ARVC via CMR.²⁰ Overdiagnosis of inherited life-threatening conditions may result in inappropriate exercise restriction and unnecessary medical procedures, such as ICD placement with its possible complications. Overdiagnosis of genetic diseases also creates unnecessary anxiety for the patient and family members.

Our clinic often changed patients' clinical management. Over 25% of patients with HCM had their medications modified and/or underwent septal reduction to mitigate LVOTO. Some of these patients were only mildly symptomatic but had reduced exercise capacity on formal exercise testing. Others have also observed that most asymptomatic or minimally symptomatic patients with HCM have diminished exercise capacity during stress exercise treadmill test.²² Patients with mild symptoms (New York Heart Association class 2) or mildly impaired exercise capacity, but severe LVOTO on exercise echocardiography, may have improved long-term outcomes with early septal myectomy.²³ We routinely perform stress exercise treadmill test and cardiopulmonary exercise stress test on patients with HCM to determine exercise capacity and the presence of latent LVOTO.

CMR is not routinely performed in patients with HCM by all general cardiologists. We routinely perform a CMR in patients with left ventricular hypertrophy to differentiate HCM from other causes of hypertrophy, to characterize their phenotype, and for risk stratification. Extensive myocardial scarring, an apical aneurysm, or severe hypertrophy found on CMR prompted an ICD placement for primary prevention in 14 of 17 patients who received a primary prevention ICD. TTE failed to detect an apical aneurysm in 4 of 6 patients with an apical aneurysm on CMR. Apical aneurysm is

an independent risk factor for sudden cardiac death in HCM and a class IIa indication for a primary prevention.¹² Apical aneurysm is also associated with increased thromboembolic risk and may require OAC.¹⁵ We routinely discuss OAC (novel oral anticoagulants (NOACs) if not contraindicated) in all patients with HCM with an apical aneurysm and no contraindications. All 6 patients chose to start OAC.

The yield of genetic testing in DCM was 24%, similar to other reports^{17–19}; however, our yield in HCM and ARVC was lower.¹⁹ This is likely attributable to our performing genetic testing on most patients referred for HCM or ARVC, even when the pretest probability was low based on the phenotype. Our practice reflects recent trends in genetic testing for IC because genetic testing is increasingly accessible and affordable.

Ninety-seven family members from 37 families had either cascade screening for a known LP/P variant identified by our clinic and/or had clinical screening because of their family risk for cardiomyopathy with us or with one of our partners. For the family members who test negative for the familial (likely) pathogenic variant, there can be a sense of relief. For those who carry the familial variant, we offer close monitoring, and they have resources available to them should they develop the disease. Preventive measurements can be taken to prevent development of diseases, such as exercise prescription for *PKP2* carriers and limited alcohol intake for *TTN* carriers. Close monitoring allows early diagnosis and interventions.

We cannot accurately estimate the rate of cascade clinical screening of family members of families with no identifiable disease-causing variants because many family members do not reside locally; however, our impression is that family screening uptake is lower with negative genetic testing. We also think that patients are more likely to screen their children than to communicate risk to their adult family members. To address this, we provide all patients with a detailed description of the condition and screening recommendations to share with family members. If a causative variant is found, we offer pretest genetic counseling and genetic testing to all first-degree family members who reside in North America.

More important, within our probands, about 50% had been diagnosed ≥ 2 years before attending our clinic and were either not given any recommendations or given incomplete recommendations for family screening (eg, only one-time screening). Furthermore, genetic counseling had not been discussed with these patients.

One of our goals is increasing the performance of autopsy, which we believe should be done in all cases of unexplained sudden death in young individuals (eg, those aged <50 years). This is currently done in several places around the globe. Furthermore, with the high

accessibility and low cost of genetic testing, molecular autopsy could be performed in all such cases. We included in this study only families with an autopsy consistent with cardiomyopathy. During the study period, we saw an additional 8 patients for FHSCD where autopsy was not performed. Unfortunately, coroners do not routinely discuss the possibility of inherited cardiovascular conditions as the cause of death and the need for family screening in such cases. We have been working with the local coroners and pathologists; however, we believe that this should be addressed on a national level.

Limitations

Our data on family screening may be incomplete, especially where family members reside out of state. As we sought to describe the first 2 years of our clinic, long-term follow-up is not included in this report. Last, the COVID-19 pandemic has likely hindered referrals to the clinic and, as such, the study time period may underestimate the full potential and impact of such clinics.

CONCLUSIONS

Specialized IC programs may improve diagnosis, management, and outcomes of patients with suspected IC and their family members. Referral of patients to a specialized clinic should be considered for all patients with (suspected) IC.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S5

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SUPPLEMENTAL MATERIAL

Table S1. Cases of changed diagnosis

Initial diagnosis	Work up	Revised diagnosis
ARVC		
<p>A 67 yo M, VT during AF ablation</p> <p>Definite ARVC based on:</p> <p>Major depolarization criteria - Epsilon wave</p> <p>Major ventricular arrhythmia criteria - VT of LBBB morphology</p> <p>Patient received an ICD for 'ARVC with ventricular arrhythmia' complicated by infection requiring extraction</p>	<p>ECG reviewed - No Epsilon wave, no TWI</p> <p>VT inconsistent with ARVC (occurred during AF ablation with ST elevation preceding the VT; VT of both RBBB and LBBB morphology)</p> <p>CMR - normal RV size (RVEDVi 77ml/m², no regional RV akinesia or dyskinesia or dyssynchronous RV contraction, mild RV dysfunction (EF 45%), No LGE</p> <p>4-generation family history - negative</p> <p>Genetic testing - negative</p>	<p>Isolated mild RV dysfunction</p> <p>Does not meet criteria for ARVC</p>
<p>A 59 yo M, NSVT during ETT</p> <p>Borderline ARVC based on:</p> <p>Major CMR criteria based on CMR performed at OSH – RVEF 39%, RV regional akinesia; RVEDVi 95ml/m²</p> <p>Minor ventricular arrhythmia criteria: NSVT with LBBB and inferior axis during ETT</p>	<p>Normal ECG</p> <p>CMR reviewed - no regional RV akinesia or dyskinesia or dyssynchronous RV contraction, normal biventricular size (LVEDVi 95ml/m², RVEDVi 86 ml/m²), mild biventricular dysfunction (LVEF 51%, RVEF 49%). No LGE.</p> <p>Holter - high burden PVC with LBBB morphology and inferior axis</p> <p>EPS – successful LVOT PVCs ablation, normal endocardial RV voltage mapping, Isopropanol challenge test - negative</p> <p>4-generation family history - negative</p> <p>Genetic testing - negative</p> <p>Repeat CMR after PVC ablation - normalization of biventricular function (LVEF 58%, RVEF 55%)</p>	<p>PVC induced cardiomyopathy</p>
<p>A 22 yo Caucasian competitive basketball player with palpitations</p> <p>Possible ARVC based on:</p> <p>Minor CMR criteria based on CMR performed at OSH - RVEDVi 114.3 mL/m² CMR, RVEF 49%, dyssynchronous RV contraction</p> <p>no LGE</p>	<p>CMR reviewed - "dyssynchronous RV contraction" is not real and secondary to RBBB</p> <p>ECG - RSR' in V1, No TWI, no epsilon wave</p> <p>Stress TTE - EF increased from 51% to 67% with exercise, GLS -19.7%</p> <p>CPET – pVO₂ 129% of predicted</p> <p>4-generation family history - negative</p>	<p>Athlete's heart</p>

<p>Minor ventricular arrhythmia criteria (>500 PVC/24hrs)</p>	<p>Genetic testing - VUS in TNNI3 Repeat CMR after 3 months of detraining – normalization of ventricular size and function (LVEDVi 103 mL/m², RVEDVi 117 mL/m², LVEF 58%, RVEF 55%), No regional RV akinesia or dyskinesia or dyssynchronous RV contraction</p>	
<p>A 51 yo M, palpitations Borderline ARVC based on: Major depolarization criteria - epsilon wave Minor CMR criteria by CMR at OSH - mild RV dysfunction, RVEF 40%, regional free wall akinesia & aneurysm, normal RV size</p>	<p>CMR reviewed - normal RV size, mildly reduced RV function, RVEF 46%, with no regional RV akinesia or dyskinesia or dyssynchronous RV contraction - does not meet criteria for ARVC ECG - RBBB with no Epsilon wave, no TWI 4-generation family history - father has DCM Genetic testing - negative</p>	<p>Isolated mild RV dysfunction Does not meet criteria for ARVC</p>
<p>A 66 yo M, PVCs Borderline ARVC based on: Minor ventricular arrhythmia criteria -sustained LBBB VT with inferior axis. EPS - VT of different morphologies from both RV&LV. Major CMR criteria - dilated RV (109.5 mL), regional dyskinesia and outpouching; mild LV dysfunction (EF 45%); myocardial edema at the epicardial border of the basal anteroseptal wall; LGE in RV insertion point, no additional LGE Normal RV volage mapping by EPS Cardiac PET study - normal Cardiac biopsy - no evidence of myocarditis, sarcoidosis or amyloidosis.</p>	<p>CMR reviewed - no regional RV akinesia or dyskinesia or dyssynchronous RV contraction ECG - low voltage, no TWI, no Epsilon wave 4-generation family history – negative Genetic testing - VUSs in LMNA and ABCC9</p>	<p>DCM Does not meet the criteria for ARVC</p>
DCM		
<p>A 26 yo athlete M, vasovagal syncope ECG – TWI in V1,2 Holter – first degree AV block, episodes of type 1 second degree AV block</p>	<p>CMR – moderately enlarged LV size (LVEDVi 128ml/m²), mild-moderate LV dysfunction (LVEF 41%), mild RV dilatation (, mild RV dysfunction (RVEF 44%), No LGE, Normal global T1 and ECV</p>	<p>Athlete’s heart</p>

<p>TTE – moderate LV dilatation (LVEDD 6cm), mild LV dysfunction (LVEF 42%), mildly dilated RV with mildly reduced function, abnormal GLS -16%</p>	<p>4-generation family history – negative Genetic testing – negative Stress TTE – LVEF increased to 67% with exercise CPET – pVO2 138% of predicted Repeat TTE after 3 months of detraining – Normal LV size (LVEDD 5.4cm) and function (LVEF 61%), normal RV size and function, normal GLS</p>	
<p>A 19 yo African American M, palpitations. ECG – ICRBB Holter – symptoms correlate with sinus rhythm and APCs TTE – mild biventricular dilatation and dysfunction (LVEDD 5.8), LVEF 46%, mild RV dilatation and dysfunction (TAPSE 16)</p>	<p>CMR – mild biventricular dilatation (LVEDVI: 116 mL/m2, RVEDVI: 129 mL/m2) and dysfunction, LVEF 48%, RVEF 46%, no regional wall motion abnormalities, LGE in the inferior RV insertion point, normal global T1 and ECV 30-day Loop monitor – no arrhythmia 4-generation family history – negative Genetic testing – negative Stress TTE – LVEF increase to 69% CPET – pVO2 max 125% of predicted Repeat CMR after 3 months of detraining – normalization of chamber size and function (LVEDVI: 103 mL/m2, RVEDVI: 117 mL/m2, LVEF 59%, RVEF 52%)</p>	<p>Athlete’s heart</p>
<p>A 26 yo Caucasian M athlete, high burden uniform PVCs (likely LVOT) and runs of NSVT Holter – frequent PVC, 23% burden Echocardiogram –LV dilatation (LVEDD 6cm), mild LV dysfunction (EF 43%), mild RV dysfunction and dilatation</p>	<p>CMR – moderately enlarged LV size (LVEDVi 128ml/m2), mild LV dysfunction (EF 41%), mild RV dilatation, mild RV dysfunction (EF 44%), No LGE ETT – suppression of PVC with exercise CPET - pVO2 133% of predicted Genetic testing – negative 4-generation family history – negative Repeat Echo post 3 months of detraining and PVC ablation – Normal LV size (LVEDD 5.4cm) and function (EF 64%), normal RV size and function</p>	<p>PVC induced cardiomyopathy and athlete’s heart</p>

HCM

<p>A 23 yo African Caribbean athlete, M, with chest pain ECG – LVH voltage criteria with TWI in V1-3 TTE – Concentric LVH, MWTH 15mm, LVEDD 57mm, EF 57%, normal diastolic parameters, normal GLS (-19.3%), LAVI 40ml/m²</p>	<p>CMR – concentric LVH, MWTH 15mm, EF 59%, LVMI 87 g/m², mild biatrial dilatation, no LGE, normal global T1 and ECV, no additional features associated with HCM* Stress TTE – no LVOT obstruction 30 day loop monitor – no arrhythmia 4-generation family history – negative Genetic testing - negative Repeat CMR after 4 months of detraining – regression of LVH, MWTH of 13mm, LVMI 80 g/m², no LGE, normal T1 and ECV</p>	<p>Athlete’s heart</p>
<p>A 31 yo African American athlete M, palpitations and SOB ECG - LVH voltage criteria and convex STE with TWI in V1-4 TTE – EF 59%, LVEDD 56mm, normal RV size and function, mild concentric hypertrophy, MWTH 13mm, normal diastolic parameters, normal GLS (-18.2%), LAVI 38ml/m² ETT – normal 24 h Holter – sinus bradycardia and rare PVCs (<1%)</p>	<p>CMR - normal biventricular size (LVEDVI 83 mL/m², RVEDVI 93 mL/m²), normal function (LVEF 57%, RVEF 53%), MWTH of 11mm, no LGE, normal native T1 and ECV, no additional features associated with HCM* Stress TTE – no LVOT obstruction 14 day Holter monitor - rare PVCs (<1%) 4-generation family history – cousin twice removed died suddenly at the age of 30 while playing basketball Genetic testing – negative</p>	<p>Athlete’s heart</p>
<p>A 43 yo M with VF arrest. Long standing HTN, LBBB. TTE - LVEF 35%; LVEDD 5.8cm CMR at outside hospital - LVEF 44%, ASH with MWTH in the mid septum of 19 mm and possible LGE in the RV insertion points</p>	<p>Repeat CMR moderately dilated LV size (LVEDVI: 124 mL/m²), LVEF 46%, normal RV size (RVEDVI: 102 mL/m²), RVEF 46%, MWTH 11mm at the anteroseptal wall, no LGE, Family history – negative Genetic testing - VUS in PKP2</p>	<p>DCM</p>
<p>A 30 yo African American M, weightlifter (~300lbs), on anabolic steroids and testosterone with secondary HTN ECG - inferolateral TWI TTE – mild concentric LVH, EF 62%, LVEDD 4.8cm, LAVI 21.8</p>	<p>Repeat CMR after 9 months of detraining, discontinuation of anabolic steroids and testosterone and blood pressure control – concentric LVH, MWTH 14mm, LVEF 58%, LVMI 81 g/m², normal RV size, RVEF 54%, LGE in the inferior RV insertion point, normal global T1</p>	<p>LVH secondary to anabolic substance abuse and athlete’s heart</p>

<p>mL/m², normal diastolic parameters, CMR – mild basal to mid anteroseptum hypertrophy, MWTH 16mm, LVEF 57%, Normal RV size, mildly reduced RV function, RVEF 49%, LVMI 94 g/m², LGE in the inferior RV insertion point, no additional features associated with HCM*</p>	<p>and ECV, no additional features associated with HCM* 7-day Holter monitor – no arrhythmia 4-generation family history – negative Genetic testing – negative</p>	
<p>A 73 yo Caucasian M, TTE – severe concentric LVH, normal LV size and function CMR – Normal LV size and function, concentric LVH, MWTH 18mm at the basal septum, mid myocardial LGE along the inferolateral basal wall and basal-mid septum (30% of the total LV mass)</p>	<p>History of bilateral carpal tunnel syndrome ECG – low voltage PYP study – positive (semi quantitative score of 3, H/CL ratio 1.52) Lab work up for AL amyloidosis – negative Family history – negative Genetic testing – negative</p>	<p>wtATTR amyloidosis</p>
<p>A 61 yo M with AF and NSVT. TTE – severe concentric LVH, MWTH 18mm, EF 65%, LAVI 25ml/m²</p>	<p>ECG – no LVH voltage criteria CMR (terminated early due to slow heart rate with frequent PVCs, no contrast given)– concentric LVH, MWTH 19mm Family history – brother has AF Genetic testing - negative PYP study - Strongly suggestive of TTR cardiac amyloidosis (semi-quantitative visual score 3 or H/CL ratio 1.83). Fused CT-SPECT imaging shows increased myocardial uptake Lab work up for AL amyloidosis – negative</p>	<p>wtATTR amyloidosis</p>
<p>A 52 yo F, long standing HTN, presyncope ECG – LBBB TTE – concentric LVH CMR – ASH, MWTH 15mm, LVEF 72%, subtle/patchy midmyocardial/epicardial LGE along the mid-basal inferior and inferolateral wall</p>	<p>Implantable loop recorder - SVT EPS – slow pathway modification, negative VT study 4-generation family history – negative Genetic testing – negative Cardiac PET study – abnormal uptake in the basal-mid lateral wall EBUS with transbronchial biopsy – non-caseating granuloma Repeat PET study after 4 months of prednisone 30mg daily– resolution of abnormal uptake</p>	<p>Cardiac sarcoidosis</p>

	Repeat CMR – no LGE, no abnormal T2, ASH, MWTH 13mm, LVEF 58%	
A 47 yo M, longstanding uncontrolled HTN, inferior STEMI. TTE – LVH; LVEDD 4.8cm, EF 55%, LAVI 17ml/m2 CMR - concentric hypertrophy, MWTH 14mm; EF 66%, transmural LGE in the basal to mid inferior wall in a vascular distribution with mild hypokinesia consistent with inferior MI, no additional LGE, no additional features associated with HCM*	Negative family history Clinical screening of parents, siblings and children - negative Genetic testing - negative ECG - inferior Q waves, no LVH voltage criteria or repolarization abnormalities	Hypertensive cardiomyopathy
64 yo African American F, long standing uncontrolled HTN. TTE – concentric LVH 1.2cm, hyperdynamic function during sinus tachycardia (HR 123bpm), SAM with LVOT gradient of 100mmHg	CMR - normal LV size and function, mild concentric LVH, MWTH 12mm, no LGE, normal global ECV 22%, no additional feature associated with HCM* TTE reviewed by us - LVOT gradient contaminated by the MR, 'true' LVOT gradient 25mmHg Repeat TTE with a HR 80bpm – function not hyperdynamic, no LVOT gradient Family history - negative Genetic testing - negative	Hypertensive cardiomyopathy
A 48 yo M, long-standing uncontrolled HTN, CKD stage 5, TTE – concentric LVH, MWTH 19mm	ECG – no LVH voltage criteria, no repolarization abnormalities, no pathological Q waves TTE reviewed by us – concentric LVH, MWTH 16mm CMR with no contrast– concentric LVH, MWTH 16mm, EF 61%, normal native T1, no additional features associated with HCM* Holter monitor – no arrhythmia 4-generation Family history – negative Clinical screening of siblings - negative, no children Genetic testing – negative (including GLA)	Hypertensive cardiomyopathy
A 71 yo F, long standing HTN TTE - LVEF 60%, ASH MWTH 15mm, LAVI 46.8ml/m2	TTE reviewed by us – true septal thickness 12mm	Sigmoid septum of the elderly and HTN

	<p>ECG – poor R wave progression in V1-3</p> <p>PYP study – negative</p> <p>4-generation family history – negative</p> <p>Children and siblings clinical screening – negative</p> <p>Genetic testing – negative</p>	
<p>A 54 yo M, long-standing uncontrolled HTN, CKD stage 3, TTE -concentric LVH, MWTH 14mm, EF 55%, 27 ml/m²</p> <p>ECG - ICRBB, no LVH voltage criteria or repolarization abnormalities</p>	<p>CMR – normal LV size and function, LVEF 61%, mild concentric LVH, MWTH 13mm, No LGE, no additional features associated with HCM*</p> <p>4-generation family history - negative</p> <p>Clinical screening of siblings - negative, no children</p> <p>Genetic testing – negative (including GLA gene)</p>	<p>Hypertensive cardiomyopathy</p>
<p>A 75 yo M, long standing HTN, shortness of breath on exertion</p> <p>TTE – normal LV size and function, EF 55%, sigmoid septum (15mm), LAVI 31.5ml/m²</p> <p>Holter monitor – short runs of NSVT, 3% PVC burden</p> <p>Exercise stress myocardial perfusion test – negative for ischemia, NSVT during recovery</p> <p>Left coronary angiogram – non obstructive coronary disease</p> <p>CMR – basal septal hypertrophy of 16mm, no LGE</p>	<p>PYP study – negative</p> <p>Lab workup for AL amyloidosis – negative, NT-pro-BNP 257</p> <p>CMR reviewed by us – sigmoid septum, true septal thickness 12mm, no LGE, no additional features associated with HCM*</p> <p>CPET – pVO₂ of 24.2, 114% of predicted</p> <p>Repeat loop monitor on beta blockers – no runs of NSVT</p> <p>4-generation family history – negative</p> <p>Genetic testing - negative</p>	<p>Sigmoid septum of the elderly and HTN</p>
<p>A 43 yo M, long standing uncontrolled HTN, CKD stage 5, AF.</p> <p>TTE – normal LV systolic function, LVEF 54%, concentric hypertrophy, MWTH 18mm, severely dilated LA (LAVI 109ml/m²)</p>	<p>ECG – no LVH voltage criteria or repolarization abnormalities</p> <p>CMR with no contrast– concentric LVH, MWTH 15mm, EF 57%, normal native T1, no additional features associated with HCM*</p> <p>4-generaitn family history – negative</p> <p>Clinical screening of siblings and son – negative</p> <p>Genetic testing – VUS in ALPK3</p>	<p>Hypertensive cardiomyopathy</p>
<p>A 25 yo African American M, familial HCM caused by a pathogenic variant in MYBC3 (c.3624dup;</p>	<p>Serial ECG showing prolonged QT interval >500ms, no identifiable reversible etiology</p> <p>Genetic testing for congenital long QT syndrome – a pathogenic variant</p>	<p>HCM and Congenital Long QT Syndrome 2</p>

p.Lys1209Glnfs*33). with VF arrest. TTE – ASH MWT 26mm. Received a SCD. Appropriate shock for polymorphic VT.	in KCNH2 (potassium voltage-gated channel subfamily H member 2) gene (c.1468G>A; p.Ala490Thr).	
iLVNC		
A 46 yo F, high burden RVOT PVCs ECG – normal, frequent PVCs (RVOT origin) TTE – normal LV size and function, hyper trabeculation of the apex, NC/C ratio 2.3 in end-systole	TTE repeated with contrast – NC/C ratio 1.8 in end-systole CMR – NC/C diameter ratio 2.1 in end-diastole, normal biventricular size and function, no LGE, normal ECV and T1 4-generation family history – negative	Hypertrabeculation

AF – atrial fibrillation; CMR – cardiac magnetic resonance; CPET – cardiopulmonary exercise test; ECV – extra cellular volume; EF – ejection fraction; ETT – exercise treadmill test; GLS – global longitudinal strain; HTN – hypertension, ICD – implantable cardioverter defibrillator; iCRBBB – incomplete right bundle branch block; LAVI – left atrial volume indexed to body surface area; LBBB – left bundle branch block; LGE – late gadolinium enhancement; LVEDD – left ventricular end diastolic diameter; LVEDVi – left ventricular end diastolic volume indexed to body surface area; LVOT – left ventricular outflow tract; NC/C – noncompaction myocardium to compaction myocardium; NSVT – non sustained VT; OSH – outside hospital; pVO2 – peak O2 consumption; PYP – pyrophosphate; RBBB – right bundle branch block; RVEDVi – right ventricular end diastolic volume indexes to body surface area RVOT – right ventricular outflow tract; TTE – transthoracic echocardiogram, TWI – T wave inversion; PVC – premature ventricular complexes; VT – ventricular tachycardia

* additional features associated with HCM: elongated mitral leaflets, abnormal chordal attachment, crypts, multiple papillary muscle heads, papillary muscle displacement, papillary muscle hypertrophy, accessory apical-septal muscle bundle

Table S2: Patients with family history for cardiomyopathy-related sudden cardiac death and no molecular autopsy

Family	Proband Diagnosis	Family member	Screening	Management
1	ARVC	27 yo female - SCD in mother, maternal aunt & cousin. Autopsy of maternal aunt consistent with ARVC	ECG - inferolateral T wave inversion; LV lateral mid wall LGE; VUS in FLNC (c.2984G>A)	Primary prevention ICD implantation. Subcutaneous ICD given young age
1	ARVC	42 yo female - SCD in mother, sister & maternal aunt. Autopsy of mother consistent with ARVC	TTE, CMR, ETT, Holter monitor - normal	Screen Q 2-3 yrs
2	ARVC with LV involvement	27 yo male - SCD in mother; ARVC with LV involvement at autopsy	TTE, CMR, ETT, Holter; normal Genetic test - negative	Screen Q 2-3 yrs
3	HCM?	39 yo male - SCD in brother; Autopsy - LV mass = 720 g, maximal wall thickness = 15 mm; no mention of myofiber disarray	TTE - concentric LV hypertrophy (15 mm); CMR - asymmetric septal hypertrophy (16mm) with mid wall LGE in the septum, genetic test - negative	Primary prevention ICD implantation
4	DCM?	30 yo male - SCD in brother; autopsy - "enlarged heart"	TTE, ECG, ETT, & Holter - normal	Screen Q 2-3 yrs

ARVC – arrhythmogenic right ventricular cardiomyopathy; CMR – cardiac magnetic resonance; DCM – dilated cardiomyopathy; HCM – hypertrophic cardiomyopathy; ICD – implantable cardioverter defibrillator; ETT – exercise treadmill; LV – left ventricle SCD – sudden cardiac death; TTE – transthoracic echocardiogram; LGE – late gadolinium enhancement

Table S3: Pathogenic/Likely Pathogenic variants by diagnosis

Diagnosis	Gene	Variant	Classification
HCM	MYBPC3	c.906-36G>A	Pathogenic
HCM	MYBPC3	c.3617delG	Pathogenic
HCM	MYH7	c.4135G>A	Pathogenic
HCM	TNNI3	c.485G>A	Pathogenic
HCM	MYBPC3	C.1972+1G>A	Likely Pathogenic
HCM	MYBPC3	c.1624G>C	Pathogenic
HCM	TNNI3	c.526G>A	Likely Pathogenic
HCM	MYBPC3*	c.3617delG	Pathogenic
HCM	MYBPC3	c.3628-41_3628-17del	Pathogenic
HCM	MYBPC3	c.1484G>A	Pathogenic
HCM	MYH7	c.1491G>T	Pathogenic
HCM	MYBPC3*	c.906-36G>A	Pathogenic
HCM	TNNI3	c.434G>A	Pathogenic
HCM	MYH7	c.2700T>G	Likely Pathogenic
HCM	ACTC1	c.301G>A	Pathogenic
HCM	MYH7	c.2555T>C	Pathogenic
HCM	MYBPC3	c.1484G>A	Pathogenic
HCM	MYBPC3	c.906-36G>A	Pathogenic
HCM	MYBPC3	c.1224-52G>A	Pathogenic

HCM	MYBPC3	c.927-2A>G	Pathogenic
HCM	ACTC1	C.310G>A	Pathogenic
HCM	GLA	c.899T>C	Pathogenic
HCM	MYBPC3	c.821+1G>A	Pathogenic
HCM	PLN	c.63_64dup	Pathogenic
HCM	MYBPC3	c.551dupT	Pathogenic
HCM	MYH7	c.1988G>A	Pathogenic
HCM	MYBPC3	c. 636C>G	Likely Pathogenic
HCM	MYBPC3	c.3624dup	Pathogenic
HCM	MYBPC3*	c.722G>A	Pathogenic
HCM	MYBPC3	c.1505G>A	Pathogenic
HCM	TNNI3	c.485G>A	Pathogenic
DCM	TTN	c.57769C>T	Likely Pathogenic
DCM	TTR*	c.424G>A	Pathogenic
DCM	DSG2	c.1481A>C	Likely Pathogenic
DCM	RBM20	c.1970G>A	Pathogenic
DCM	TTR	c.424G>A	Pathogenic
DCM	TTN	c.66160+2T>C	Likely Pathogenic
DCM	FLNC	c.6240_6259del	Pathogenic
DCM	RBM20	c.1913C>T	Pathogenic
DCM	TTN	c.93956C>A	Likely Pathogenic
DCM	TTN	c.80268_80269del	Likely Pathogenic
DCM	FLNC*	c.6240_6259del	Pathogenic

DCM	BAG3	c.331_332del	Pathogenic
DCM	LMNA	c.232A>G	Likely Pathogenic
DCM	DES	c.1360C>T	Pathogenic
ARVC	PKP2	c.1237C>T	Pathogenic
ARVC	PKP2*	c.1034+1G>T	Pathogenic
ARVC	PKP2	c.2146-1G>C	Pathogenic
iLVNC	TTN	c.83064_83073del	Likely Pathogenic
FHSUD	FLNC*	c.5199+1G>T	Likely Pathogenic
FHSUD	FLNC*	c.5199+1G>T	Likely Pathogenic
FHSUD	PKP2*	c.1489C>T	Likely Pathogenic

ARVC – arrhythmogenic right ventricular cardiomyopathy; DCM – dilated cardiomyopathy;
FHSCD – family history of sudden cardiac death; HCM – hypertrophic cardiomyopathy; iLVNC –
isolated left ventricular non compaction

* Family cascade testing; not counted in overall yield

**Homozygous variant

Table S4: Variants of uncertain significance by diagnosis

Diagnosis	Gene	Variant
HCM	MYH6	c.2614C>T
HCM	MYBPC3	c.3124A>G
HCM	RBM20	c.1766G>A
HCM	TNNT2	c.832C>T
HCM	DSP	c.5167G>C
HCM	JUP	c.2069A>G
HCM	PKP2	c.950C>T
HCM	DSP	c.8014C>G
HCM	TTN	c.107836C>T
HCM	DSG2	c.1374_1388del
HCM	BAG3	c.679C>G
HCM	RYR2	c.3151C>T
HCM	DSP	c.3706A>G
HCM	FLNC	c.2086T>C
HCM	KCNJ2	c.1199C>T
HCM	DES	c.1158C>T
HCM	FLNC	c.6923C>T
HCM	MYH7	c.2926A>G
HCM	JUP	c.1400C>T
HCM	LMNA*	c.1424A>G

HCM	DSP	c.542+5G>A
DCM	DSC2	c.23G>T
DCM	PRKAG2	c.320C>T
DCM	RYR2	c.12589A>G
DCM	MYBPC3	c.2682G>T
DCM	DSC2	c.1239T>G
DCM	DSC2	c.2807C>T
DCM	DSC2	c.508T>C
DCM	TNNI3	c.322G>A
DCM	DSP	c.2386G>A
DCM	MYH7	c.3982G>A
DCM	RYR2	c.3320 C>T
DCM	FLNC	c.2491G>A
DCM	MYBPC3	c.529C>T
DCM	MYBPC3	c.1321G>A
DCM	PKP2	c.1576A>G
DCM	TPM1	c.797A>G
DCM	DSP	c.6067G>T
DCM	FLNC	c.3133C>A
DCM	MYL4	c.365A>G
DCM	RBM20	c.1603G>A
DCM	TNNC1	c.202G>A
DCM	FLNC	c.2635C>T

DCM	FLNC	c.4334A>G
DCM	RYR2	c.5652_5653delinsTT
DCM	MYH7*	c.121G>A
DCM	TTN	c.103486A>G
DCM	ACTN2	c.113A>G
DCM	MYH7	c.5248A>G
DCM	RYR2	c.6792G>T
ARVC	TNNI3	c.406C>T
ARVC	LMNA	c.937-7C>G

ARVC – arrhythmogenic right ventricular cardiomyopathy; DCM – dilated cardiomyopathy; HCM – hypertrophic cardiomyopathy

*Family VUS resolution, not counted in overall yield

Table S5: Patients with dilated cardiomyopathy and Pathogenic/Likely Pathogenic variants in arrhythmogenic genes

Proband	Presentation	Genetic testing	Management
32 yo male	AF with rapid ventricular response and severe LV dysfunction	<i>LMNA</i> (c.232A>G) classified by the commercial lab as a VUS. Reviewing the available data, we felt that this is likely a disease-causing variant*. Parents do not carry the variant consistent with de-novo variant further supporting the variant's pathogenicity	GDMT for HFrEF, Amiodarone for rhythm control, primary prevention ICD despite GDMT for only 2 weeks. To undergo AF ablation.
38-year-old male	Acute HFrEF, severe LV dysfunction	Pathogenic <i>FLNC</i> variant (c.6240-6259del)	Primary prevention ICD despite GDMT for only 4 weeks
28-year-old male	Complete heart block, normal TTE; normal GDP PET uptake. CMR - normal RV & LV size and function, mild mid wall septal LGE. Dual chamber pacemaker implantation	Known <i>Desmin</i> gene pathogenic variant (c.1360C>T) associated with ventricular arrhythmias, cardiomyopathy, and death. ¹⁵	Dual chamber pacemaker upgrade to a BiV ICD

* A rare conversed variant located in a mutational hot spot, a different amino acid change has been shown to be pathogenic; the variant had been reported before in a case report of a similar phenotype

AF – atrial fibrillation; CMR – cardiac magnetic resonance; GDMT – guideline directed medical therapy; ETT – exercise treadmill test; HFrEF – heart failure with reduced ejection fraction; ICD – implantable cardioverter defibrillator; LGE – late gadolinium enhancement; TTE – transthoracic echocardiogram; VUS – variant of uncertain significance