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Rare Variant Genetics and Dilated Cardiomyopathy Severity: The DCM Precision Medicine Study

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BACKGROUND: Dilated cardiomyopathy (DCM) can lead to advanced disease, defined herein as necessitating a durable left ventricular assist device or a heart transplant (LVAD/HT). DCM is known to have a genetic basis, but the association of rare variant genetics with advanced DCM has not been studied.

METHODS: We analyzed clinical and genetic sequence data from patients enrolled between 2016 and 2021 in the US multisite DCM Precision Medicine Study, which was a geographically diverse, multiracial, multiethnic cohort. Clinical evaluation included standardized patient interview and medical record query forms. DCM severity was classified into 3 groups: patients with advanced disease with LVAD/HT; patients with an implantable cardioverter defibrillator (ICD) only; or patients with no ICD or LVAD/HT. Rare variants in 36 DCM genes were classified as pathogenic or likely pathogenic or variants of uncertain significance. Confounding factors we considered included demographic characteristics, lifestyle factors, access to care, DCM duration, and comorbidities. Crude and adjusted associations between DCM severity and rare variant genetic findings were assessed using multinomial models with generalized logit link.

RESULTS: Patients' mean (SD) age was 51.9 (13.6) years; 42% were of African ancestry, 56% were of European ancestry, and 44% were female. Of 1198 patients, 347 had LVAD/HT, 511 had an ICD, and 340 had no LVAD/HT or ICD. The percentage of patients with pathogenic or likely pathogenic variants was 26.2%, 15.9%, and 15.0% for those with LVAD/HT, ICD only, or neither, respectively. After controlling for sociodemographic characteristics and comorbidities, patients with DCM with LVAD/HT were more likely than those without LVAD/HT or ICD to have DCM-related pathogenic or likely pathogenic rare variants (odds ratio, 2.3 [95% CI, 1.5–3.6]). The association did not differ by ancestry. Rare variant genetic findings were similar between patients with DCM with an ICD and those without LVAD/HT or ICD.

CONCLUSIONS: Advanced DCM was associated with higher odds of rare variants in DCM genes adjudicated as pathogenic or likely pathogenic, compared with individuals with less severe DCM. This finding may help assess the risk of outcomes in management of patients with DCM and their at-risk family members.

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Key Words: cardiomyopathy, dilated ■ genetics ■ risk

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Clinical Perspective

What Is New?

- This multisite study of patients with dilated cardiomyopathy (DCM) compared 3 DCM severity groups (left ventricular assist device or heart transplant [LVAD/HT], implantable cardioverter defibrillator [ICD] only, or neither [no ICD or LVAD/HT]) and found that patients with LVAD/HT were more than twice as likely to carry a rare variant in a DCM gene classified as pathogenic or likely pathogenic compared with patients with DCM without LVAD/HT.
- This study was the first to recruit a large number of patients with DCM with LVAD/HT and diverse genomic ancestry from geographically diverse heart failure programs and provides evidence to highlight the role for genetic testing to assist in the genetic risk assessment of patients with advanced DCM and their families.

What Are the Clinical Implications?

- These findings are highly relevant because >1 in 4 patients with advanced disease had actionable genetic findings, providing compelling indications for genetic testing of their first-degree relatives (ie, parents, siblings, children) to assess their genetic risk of DCM.
- Results from this study provide additional insight for clinicians who provide care to patients with DCM in disease management and outcome assessment, which applies to patients of African ancestry as well as patients of European ancestry.

Nonstandard Abbreviations and Acronyms

DCM	dilated cardiomyopathy
ICD	implantable cardioverter defibrillator
LVAD/HT	left ventricular assist device or heart transplant
LVEF	left ventricular ejection fraction
P/LP	pathogenic or likely pathogenic
VUS	variant of uncertain significance

Risk predictors for dilated cardiomyopathy (DCM) outcomes remain difficult to personalize for patients and their families because of the heterogeneity of DCM presentation,[1] especially for advanced disease, defined herein as requiring a durable left ventricular assist device or a heart transplant (LVAD/HT). Although patients with familial DCM may present at an earlier age,[2] the rare variant genetics associated with advanced disease from DCM are understudied. Of 4 case series of patients with advanced DCM and genetic sequence analysis, one reported 30 patients,[3] most having had LVAD/HT, with 51% having a pathogenic variant considered to explain their disease. In three additional case series, all with patients who had undergone cardiac transplantation, 1 included 52 familial patients with DCM with a yield of 40% pathogenic variants.[4] Another study reported 13 patients, of whom 8 had familial DCM, with a yield of 1 likely pathogenic *LMNA* variant.[5] Another study reported 10 of 26 (38%) patients with DCM who had pathogenic variants.[6]

Numerous other recent helpful DCM genetics studies with larger numbers of patients have been published,[2,3,7–12] but these studies had few patients with advanced disease or were limited by patient selection on the basis of analysis of specific genes[7,9,11,12] or sequence availability,[10] or by a study design focused on reverse remodeling not conducive to inclusion of advanced cases of DCM.[8] Moreover, most had no information regarding race or ethnicity,[2,3,7,8,10–12] or if information regarding race was provided,[9] had very few non-White participants.

DCM that leads to the need for LVAD/HT can cause considerable clinical, psychological, and care burdens for patients and their relatives. Understanding the association of rare variant genetics with DCM outcomes can help assess the risk of DCM for family-based management, guide genetic counseling about genetic and environmental exposures that may worsen the disease, and support the early identification of family members with asymptomatic disease. Also, the effect of self-determined race on DCM outcomes has been suggested to be relevant. Black patients with DCM have been reported to have earlier onset with more familial disease[13] and worse outcomes than White patients,[14,15] but, as noted, most reports regarding DCM severity and genetics have not specified race or ancestry.

The multisite DCM Consortium Study recruited a large number of patients with DCM in a geographically representative, multiracial, and multiethnic cohort between 2016 and 2021.[13,16] This analysis aimed to assess the role of rare variant genetics in DCM severity, including the clinical characteristics of patients with DCM with LVAD/HT, implantable cardioverter defibrillator (ICD) only, or neither (no ICD or LVAD/HT), while controlling for other influential factors related to patient outcomes.

METHODS

The data from this article are available at dbGaP (the database of Genotypes and Phenotypes) and can be accessed at www.ncbi.nlm.nih.gov/gap.

The DCM Precision Medicine Study

The DCM Precision Medicine Study aimed to test the hypothesis that DCM has a substantial genetic basis and to evaluate the effectiveness of a family communication intervention in improving the uptake of family member clinical screening.[16,17]

The study recruited 1265 patients with DCM (probands) and nearly 2000 of their relatives.[13] Probands were patients identified by heart failure or heart transplant cardiologists and clinical research personnel in heart failure and heart transplant programs at multiple sites in the DCM Consortium from across the United States.[13] The institutional review boards at The Ohio State University and all clinical sites approved the initial study, followed by single institutional review board oversight at The University of Pennsylvania. All participants gave written informed consent. This analysis used data from all eligible patients with DCM ≥15 years of age (n=1198; Figure 1). Study inclusion and exclusion criteria have been reported previously.[13,16] The data that support the findings of this study are available from the corresponding author upon reasonable request.

DCM Diagnosis and Severity

All probands met diagnostic criteria for DCM, which included left ventricular systolic dysfunction, defined by a left ventricular ejection fraction (LVEF) <50%, and left ventricular enlargement, defined by a left ventricular internal diastolic dimension >95th percentile for height and sex,[18] with other usually detectable clinical causes excluded, as defined previously.[13,16] Available cardiac magnetic resonance imaging data were used to validate the study's DCM phenotype and exclude other clinically identifiable pathogeneses.[19]

Clinical data were centrally adjudicated to establish whether idiopathic DCM was present. Central adjudication was performed by The Ohio State University site principal investigator. All clinical data were interpreted without knowledge of family relationships or genetic information.

Patients with DCM were classified into 3 severity groups: advanced DCM (LVAD/HT), ICD only, or neither (no ICD or LVAD/HT). The latter 2 groups were defined collectively as not advanced DCM. The ICD group was selected because the presence or absence of an ICD could be conclusively determined, and most patients with DCM in the United States with ICDs compared with those with no ICD had either an arrhythmic substrate (for secondary prevention) or a longer period of reduced LVEF despite medical therapy (for primary prevention).

Genetic Data Collection

Research exome sequencing and array-based genotyping of individuals with DCM diagnoses were conducted at the University of Washington Genome Sciences, and genomic data files were transferred to the Division of Human Genetics Data Management Platform at the Ohio Supercomputer Center for further analysis of a panel of 36 genes considered clinically relevant for DCM[20,21] (Table S1). Variants were adjudicated using American College of Medical Genetics[22] and ClinGen-based criteria tailored to DCM[20] and assigned to an American College of Medical Genetics category: pathogenic or likely pathogenic

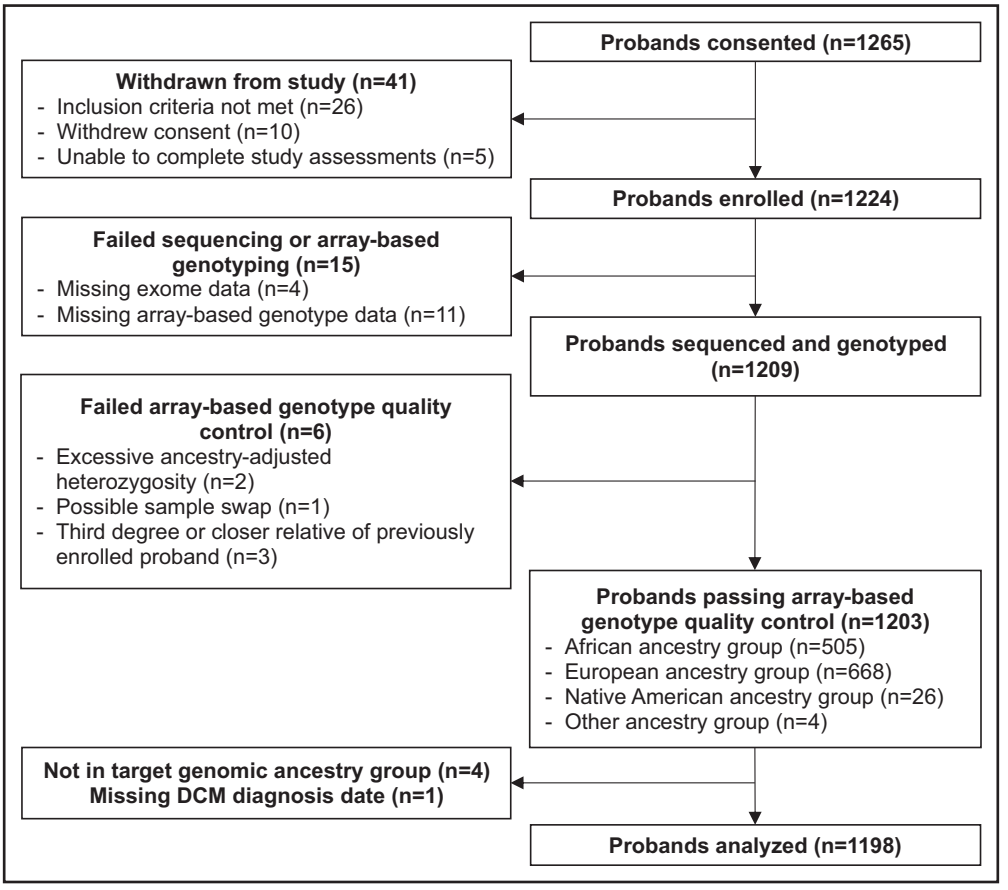


Figure 1. DCM Precision Medicine Study recruitment and analysis.
DCM indicates dilated cardiomyopathy.

(P/LP) or variant of uncertain significance (VUS). P/LP and VUS were confirmed by Sanger sequencing.

Demographic and Other Clinical Information Collected

Structured interviews collected patient sociodemographic characteristics (eg, age at enrollment, sex, years of education, tobacco use), self-reported medical history, and health care coverage information; medical record questionnaires validated and summarized key cardiovascular clinical information. Duration of DCM was calculated from the date of DCM diagnosis or date of LVAD/HT (whichever came first) for patients with LVAD/HT; for patients with ICD only or neither, the DCM duration was on the basis of diagnosis date and enrollment date. Geographic location of study sites was grouped by region (Northeast, Midwest, South, and West).

The DCM Consortium is aware of issues[23] in the collection, analysis, presentation, and discussion of race, ethnicity, and ancestry and has adopted recommended approaches.[24–27] This study examined whether the association between DCM severity and rare variant genetic findings differed by genomic ancestry. Global genomic ancestry proportions were inferred from Illumina Global Screening Array genotypes using ADMIXTURE software[28] with the 1000 Genomes Phase 3 integrated call set as the reference.[21] An individual's ancestry was defined as the continental ancestry group (African, East Asian, European, Native American, or South Asian) accounting for the highest proportion of his or her genomic ancestry. Individuals with ancestry other than African, European, or Native American were not analyzed because of small numbers (n=4).

Race and ethnicity data, which were also included in this study because of their relevance for health outcomes, were self-reported by participants using structured race (Native American or Alaska Native, Asian, African American, Native Hawaiian or Pacific Islander, White, more than one race, or unknown) and Hispanic ethnicity (yes, no, or unknown) categories. Because genomic ancestry in these study participants is highly correlated to self-reported race and ethnicity (Table S2), the results may be generalizable to clinical practice settings where self-reported information is the sole source for race and ethnicity definition.

Statistical Analysis

Characteristics of patients in the 3 DCM severity groups were compared by subgroups of sociodemographic and clinical characteristics with means and SDs if normally distributed or medians and interquartile ranges if not normally distributed. Continuous variables were categorized if they were not linearly associated with the outcome. Crude and adjusted associations between DCM severity and the most deleterious DCM-related rare variant found (P/LP, VUS only, or negative) were examined using multinomial models with generalized logit link in which the dependent variable was DCM severity status and the independent variable of interest was the most deleterious DCM-related rare variant found. On the basis of the literature review, confounding factors considered included any factors, other than genetic findings, that may associate with DCM occurrence and outcomes, including sociodemographic variables (eg, sex, ancestry, education, tobacco use), health care access and care quality (eg, health insurance coverage, geographic region of study sites), DCM duration, and comorbidities. We did not control for age at diagnosis because it is known to be associated with genetic susceptibility, and including it in the model might adjust the genetic effect away.

Three statistical models were developed to assess the associations between DCM severity (LVAD/HT or ICD only, with neither as reference group) and presence of DCM-related rare variants (P/LP, VUS only, or negative). Model 1 examined the crude association, including only a fixed effect for the rare variant group; model 2 also adjusted for social, demographic, and health care–related variables that modified the association; and model 3 additionally adjusted for DCM duration and comorbidities. Odds ratios and 95% CIs were estimated on the basis of multinomial models with generalized logit link. The interaction between presence of DCM-related rare variant group and genomic ancestry (African versus European ancestry) was examined in model 3 after excluding patients with Native American ancestry because of its small numbers. A 2-sided P value of <0.05 was considered to indicate statistical significance in all tests. All analyses were performed in R version 4.1.1 (R Foundation) and SAS/STAT 15.2 software, version 9.4 (TS1M7), of the SAS System for 64-bit Windows (SAS Institute).

RESULTS

Patients' mean (SD) age was 51.9 (13.6) years; 42% were of African ancestry, 56% were of European ancestry, and 44% were female; high correlation was noted with self-identified race, with 43.0% Black patients and 56.8% White patients (Table 1). Of 1198 patients, 347 (29.0%) had LVAD/HT, 511 (42.7%) had an ICD only, and 340 (28.3%) had no LVAD/HT or ICD. Of the 511 patients with an ICD, 96 also had a biventricular pacemaker; 8 patients who had neither an ICD nor LVAD/HT had a biventricular pacemaker. Overall, 223 (18.6%) patients harbored P/LP variants in high-evidence DCM-associated genes, and 515 (43.0%) harbored VUS only, with minimal difference by age (Tables S1 and S3).

Table 1 presents sociodemographic and clinical characteristics of patients with DCM for the 3 DCM severity groups. Patients with DCM with LVAD/HT tended to be younger at diagnosis and were more likely to be male, to be self-reported as Hispanic or Black or classified with African ancestry, to have had ≤12 years of education, and to reside in the South or West compared with those with an ICD or no LVAD/HT or ICD. Patients with DCM with LVAD/HT also had higher left ventricular internal diastolic dimensions and lower LVEFs; were more likely to have comorbidities such as atrial fibrillation, diabetes, or hypertension; and were more likely to have had a history of heart failure. Compared with patients with no LVAD/HT/ICD, patients with ICD only were more likely to have had a history of arrhythmia or conduction system disease (53.2% versus 23.2%) or sudden cardiac death (7.6% versus 0.6%). The no LVAD/HT/ICD group also had overall milder disease compared with the ICD group, with shorter duration of disease, less left ventricular enlargement, a higher LVEF, and less history of heart

Table 1. Demographic and Clinical Characteristics of Patients With DCM by DCM Severity (With Durable LVAD/HT, ICD Only, or None)

Variable	With LVAD/HT	With ICD	Neither	Total
Total number	347 (100.0)	511 (100.0)	340 (100.0)	1198 (100.0)
Age at diagnosis, y	41.5±12.9	45.5±13.1	44.9±14.4	44.2±13.5
Age at enrollment, y	51.6±13.4	53.5±13.0	49.8±14.3	51.9±13.6
Female	120 (34.6)	237 (46.4)	167 (49.1)	524 (43.7)
Self-reported race or ethnicity				
Hispanic	31 (8.9)	44 (8.6)	27 (7.9)	102 (8.5)
Black	162 (46.7)	218 (42.7)	135 (39.7)	515 (43.0)
White	185 (53.3)	291 (56.9)	205 (60.3)	681 (56.8)
Other	0	2 (0.4)	0	2 (0.2)
Genomic ancestry				
African	159 (45.8)	212 (41.5)	134 (39.4)	505 (42.2)
European	176 (50.7)	292 (57.1)	199 (58.5)	667 (55.7)
Native American	12 (3.5)	7 (1.4)	7 (2.1)	26 (2.2)
Education, y				
≤12	147 (44.7)	194 (40.6)	104 (32.6)	445 (39.5)
>12	182 (55.3)	284 (59.4)	215 (67.4)	681 (60.5)
Missing	18	33	21	72
US region of study site				
Northeast	42 (12.1)	70 (13.7)	38 (11.2)	150 (12.5)
Midwest	86 (24.8)	186 (36.4)	135 (39.7)	407 (34.0)
South	145 (41.8)	192 (37.6)	122 (35.9)	459 (38.3)
West	74 (21.3)	63 (12.3)	45 (13.2)	182 (15.2)
DCM duration, y				
<5	167 (48.3)	235 (46.0)	239 (70.3)	641 (53.6)
≥5	179 (51.7)	276 (54.0)	101 (29.7)	556 (46.4)
Missing	1	0	0	1
Echocardiographic findings*				
LVIDD, mm	68.6±8.6	65.6±8.0	62.6±6.8	65.6±8.2
LVIDD z score†	4.8±1.9	4.4±1.7	3.8±1.4	4.3±1.7
LVEF	20.0 (8.0)	20 (15.0)	25.0 (14.5)	20.0 (14.0)
ECG findings				
Atrial fibrillation	25 (7.3)	29 (5.7)	18 (5.3)	72 (6.0)
First-degree AV block	30 (8.7)	34 (6.7)	13 (3.8)	77 (6.5)
Second-degree AV block	1 (0.3)	0	0	1 (0.1)
Third-degree AV block	0	0	0	0
LBBB	21 (6.1)	84 (16.4)	49 (14.5)	154 (12.9)
RBBB	16 (4.7)	18 (3.5)	9 (2.7)	43 (3.6)
Comorbidity				
Diabetes	118 (34.0)	118 (23.1)	62 (18.2)	298 (24.9)
Hypertension	201 (57.9)	274 (53.6)	160 (47.1)	635 (53.0)
Medical history				
Heart failure	344 (99.1)	440 (86.1)	269 (79.1)	1053 (87.9)
Arrhythmias or conduction system disease	206 (59.4)	278 (54.4)	99 (29.1)	583 (48.7)
Stroke	9 (2.6)	13 (2.5)	10 (2.9)	32 (2.7)
Sudden cardiac death	18 (5.2)	39 (7.6)	2 (0.6)	59 (4.9)

(*Continued*)

Table 1. Continued

Variable	With LVAD/HT	With ICD	Neither	Total
Tobacco use (ever)	144 (41.7)	204 (40.0)	132 (38.9)	480 (40.2)
Missing	2	1	1	4
Health insurance coverage	313 (92.9)	428 (86.1)	297 (90.0)	1038 (89.2)
Missing	10	14	10	34

Values are mean±SD, n (%), or median (interquartile range). AV indicates atrioventricular; DCM, dilated cardiomyopathy; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; LVAD/HT, left ventricular assist device or heart transplant; and RBBB, right bundle branch block.

*A total of 1170 left ventricular internal diastolic dimension (LVIDD) values and 1172 left ventricular ejection fraction (LVEF) values are from echocardiography; 22 LVIDD values and 21 LVEF values are from cardiac magnetic resonance imaging.

†Calculated on the basis of sex and height for all study participants with heights of at least 152 cm (male) or 137 cm (female).

failure. The history of arrhythmias or conduction system disease, or history of sudden cardiac death, both suggest milder disease in the no LVAD/HT/ICD group.

Table 2 and Figure 2 present the most deleterious DCM-related rare variant found by DCM severity status for patients with DCM overall and for patients of African and European ancestry. The percentage of patients with P/LP variants was higher for those with LVAD/HT compared with those with ICD and no LVAD/HT/ICD (26.2%, 15.9%, and 15.0%, respectively). This pattern was seen in patients of African ancestry as well as patients of European ancestry. For all 3 DCM severity groups, the percent with P/LP variants was lower in patients of African ancestry than in patients of European ancestry as previously reported.[21] The list of variants is presented by age at DCM diagnosis (<45 or ≥45 years) for patients with LVAD/HT (Table S3).

Table 3 presents the crude and adjusted associations between DCM severity status and presence of DCM-related rare variants. Compared with those without LVAD/HT or ICD, patients with LVAD/HT were more likely to have P/LP variants (odds ratio, 1.9 [95% CI, 1.2–2.8]; model 1). After the adjustment for sociodemographic variables, the odds ratio increased to 2.2 (95% CI, 1.4–3.3; model 2). The odds ratio increased slightly to 2.3 (95% CI, 1.5–3.6) after additionally controlling for DCM duration, diabetes, and hypertension. The association did not differ by African or European ancestry ($P_{interaction}$= 0.16). The presence of VUS only was not statistically different between those with ICD only and those without ICD or LVAD/HT.

DISCUSSION

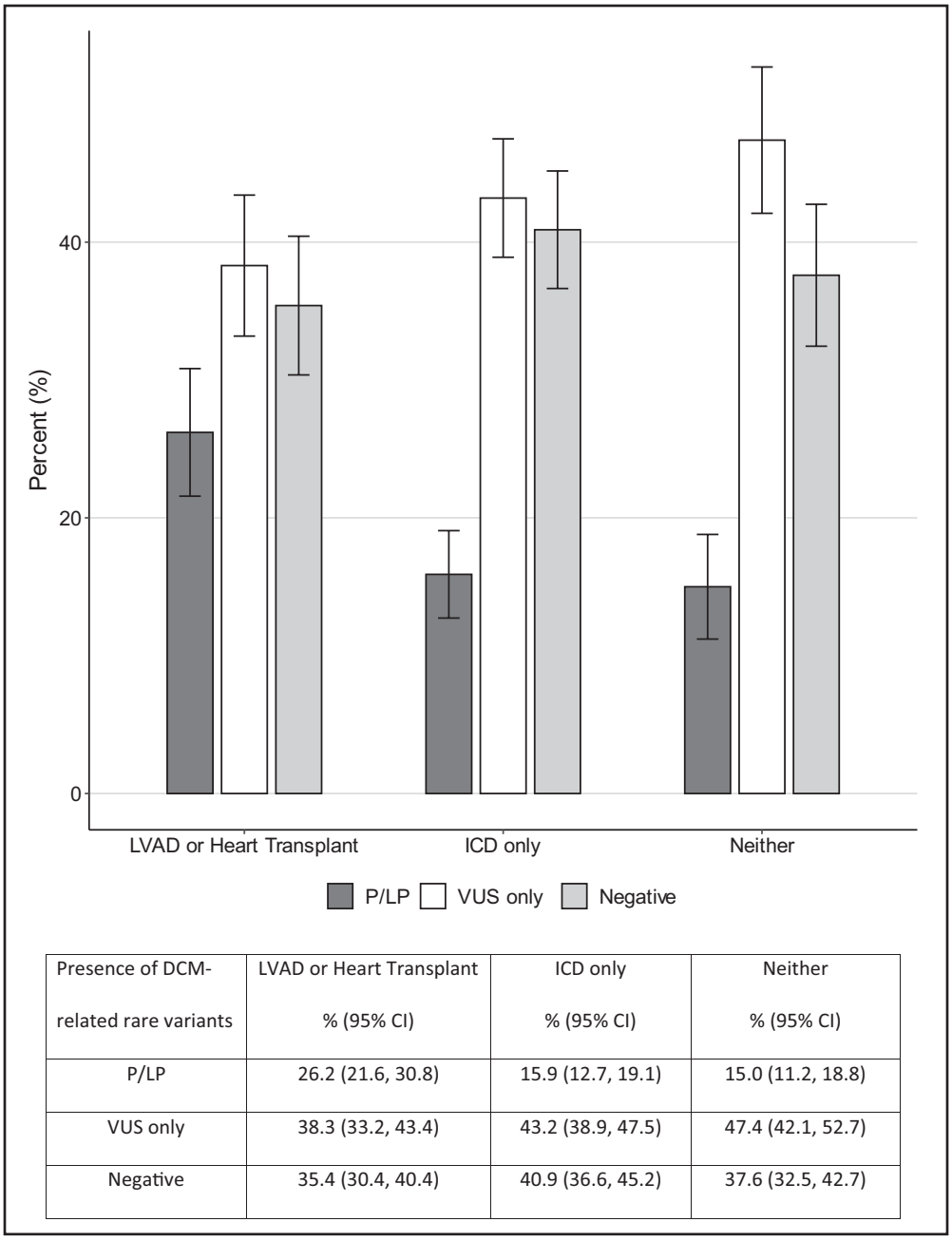
From this multisite study of carefully phenotyped patients with DCM, those who had advanced DCM, defined as having had a LVAD/HT, were more than twice as likely to carry a rare variant in a DCM gene classified as pathogenic or likely pathogenic compared with patients with DCM without advanced disease. This finding was observed in patients with DCM of African or European ancestry, after controlling for the effects of sociodemographic factors,

Table 2. Most Deleterious DCM-Related Rare Variant (P/LP and VUS) Found in Patients With Idiopathic Cardiomyopathy by DCM Severity (With LVAD/HT, ICD, or None)

Presence of DCM-related rare variants	Total	LVAD/HT (n=347)	ICD (n=511)	Neither (n=340)	*P* value*
Overall					<0.001
P/LP	223 (18.6)	91 (26.2)	81 (15.9)	51 (15.0)	
VUS only	515 (43.0)	133 (38.3)	221 (43.2)	161 (47.4)	
Negative	460 (38.4)	123 (35.4)	209 (40.9)	128 (37.6)	
African ancestry					0.08
P/LP	44 (8.7)	21 (13.2)	12 (5.7)	11 (8.2)	
VUS only	247 (48.9)	69 (43.4)	114 (53.8)	64 (47.8)	
Negative	214 (42.4)	69 (43.4)	86 (40.6)	59 (44.0)	
European ancestry					<0.001
P/LP	171 (25.6)	65 (36.9)	68 (23.3)	38 (19.1)	
VUS only	259 (38.8)	60 (34.1)	105 (36.0)	94 (47.2)	
Negative	237 (35.5)	51 (29.0)	119 (40.8)	67 (33.7)	

Values are n (%). ICD indicates implantable cardioverter defibrillator; LVAD/HT, left ventricular assist device or heart transplant; P/LP, pathogenic or likely pathogenic; and VUS, variant of uncertain significance.

**P* value is on the basis of the χ^2 test that compares distributions of the dilated cardiomyopathy (DCM)–related variant group by the 3 DCM severity groups.



Presence of DCM-related rare variants	LVAD or Heart Transplant % (95% CI)	ICD only % (95% CI)	Neither % (95% CI)
P/LP	26.2 (21.6, 30.8)	15.9 (12.7, 19.1)	15.0 (11.2, 18.8)
VUS only	38.3 (33.2, 43.4)	43.2 (38.9, 47.5)	47.4 (42.1, 52.7)
Negative	35.4 (30.4, 40.4)	40.9 (36.6, 45.2)	37.6 (32.5, 42.7)

Figure 2. Most deleterious DCM-related rare variant by DCM severity status.
Percent distributions of patients by their most deleterious dilated cardiomyopathy (DCM)–related rare variant (pathogenic or likely pathogenic [P/LP], variant of uncertain significance [VUS] only, or negative) and DCM severity status (left ventricular assist device [LVAD] or heart transplant, implantable cardioverter defibrillator [ICD] only, or neither). The percentage of patients with P/LP variants was higher for those with LVAD or heart transplant compared with those with ICD and none (26.2%, 15.9%, and 15.0%, respectively; $P<0.001$).

geographic region of study sites, major comorbidities, and DCM duration. This is clinically highly relevant as the study provides additional insight for clinicians who provide care to patients across the spectrum of disease, and especially for those who progress to advanced disease and inclusive of patients of African ancestry.

Clinical relevance of these findings is amplified when considering the opportunity to prevent DCM in at-risk family members of patients with advanced DCM, as >1 in 4 (91 of 347 [26.2%]) had a P/LP genetic result. Such P/LP results are actionable clinical genetics findings for first-degree relatives to assess their DCM risk. Nearly every cardiac transplant program has anecdotal examples of a sibling or offspring of a previously transplanted patient who presented with advanced heart failure and underwent cardiac transplantation. The data presented here may be sufficiently compelling that such occurrences can be prevented by the implementation of well-vetted genetic cardiomyopathy guidelines by cardiac transplantation programs.[29–31] Implementation of

Table 3. Association of DCM Severity With the Most Deleterious DCM-Related Rare Variant Found

DCM-related rare variants	LVAD or heart transplant versus neither, OR (95% CI)	With ICD versus neither, OR (95% CI)
Model 1: crude		
P/LP	1.9 (1.2, 2.8)	1.0 (0.6, 1.5)
VUS only	0.9 (0.6, 1.2)	0.8 (0.6, 1.1)
Negative	Reference	Reference
Model 2: controlled for demographic and social determinants*		
P/LP	2.2 (1.4, 3.3)	1.0 (0.7, 1.5)
VUS only	0.9 (0.6, 1.2)	0.8 (0.6, 1.1)
Negative	Reference	Reference
Model 3: additionally controlled for factors affecting disease severity†		
P/LP	2.3 (1.5, 3.6)	1.0 (0.6, 1.5)
VUS only	0.8 (0.6, 1.2)	0.8 (0.6, 1.1)
Negative	Reference	Reference

Estimates are on the basis of multinomial models with generalized logit link. Response variable is unordered and "neither" (ie, with no left ventricular assist device [LVAD], heart transplant, or implantable cardioverter defibrillator [ICD]) is the reference group. P/LP indicates pathogenic or likely pathogenic; and VUS, variant of uncertain significance.

*Model 2 controlled for genomic ancestry (African ancestry, European ancestry, or Native American), US region of study sites, and tobacco use (ever or not). Adjustment for sex, education (≤12 or >12 years), and health insurance coverage (yes or no) did not alter the estimated odds ratios (ORs) for the dilated cardiomyopathy (DCM)–related rare variant groups.

†Model 3 controlled for DCM duration (<5 or ≥5 years) and comorbidities (eg, diabetes, hypertension) in addition to sociodemographic variables controlled in model 2. There was no statistical interaction between ancestry (African or European) and DCM-related rare variant group (P=0.15) when patients with Native American ancestry were excluded.

such guidelines would include the routine genetic testing of patients with DCM requiring LVAD/HT, followed by clinical evaluation of all first-degree relatives for DCM, including cascade genetic testing of first-degree relatives of probands found to harbor P/LP variants.

A key aspect that distinguishes this study from others that have assessed genetic findings in patients with DCM was its design and systematic implementation across 25 US clinical sites that provide advanced heart failure and cardiac transplantation care. The patients who participated were not selected on the basis of availability of previously obtained genetic testing findings or an established history of familial DCM; rather, site principal investigators were requested to enroll a diverse sample of patients with DCM across the disease spectrum and widely representative of all patients seen at heart failure and cardiac transplantation programs to test the general hypothesis that most DCM cases have a genetic basis. Also, because this was a randomized study for the return of genetic results,[17] most patients enrolled had not had previous genetic testing. These conditions taken together suggest that this cohort may be representative of most patients seen at US advanced heart failure programs.

The analysis of DCM clinical severity is challenging; at diagnosis, the disease trajectory of DCM is unpredictable, and no single clinical measure or biomarker can summarize overall risk. Although most patients with DCM present in heart failure, and many with fully decompensated heart failure, some will show prompt and substantial improvement with medical therapy, whereas others will show minimal favorable responses.[7–9,12] One of 3 outcomes ultimately occurs: stabilization with sustained improvement; stabilization with minimal improvement; or eventual deterioration, including progressive heart failure and consideration of advanced therapies. For this cross-sectional study, DCM severity was classified by assigning probands into 1 of 3 categories: those who had received advanced therapies (LVAD/HT), those who had received an ICD, or those who had received none of those interventions. The ICD classification was selected because the presence or absence of an ICD could be unambiguously identified; in the United States, patients with DCM who are provided ICDs for primary prevention are required to have sustained left ventricular dysfunction, with a LVEF <35% for several months after the institution of medical therapy,[31] suggesting that such a cohort may have had more advanced disease than patients with DCM who had not received an ICD; and patients who needed an ICD for secondary prevention may represent an overall sicker cohort than patients who have never had sudden cardiac death or sustained ventricular arrhythmias. The ICD group and the no ICD or LVAD/HT group were clinically distinctive from one another, as the no ICD or LVAD/HT group, as noted previously, had multiple measures of less advanced disease, validating the general approach for this analysis. Nevertheless, the use of this classification is imperfect, as some patients who might have qualified for advanced therapies on the basis of medical criteria could have been precluded from such treatment because of nonmedical issues. Moreover, the provision of advanced therapies may suffer from race-related bias,[32,33] although an earlier study suggested improved trends for VAD use in self-identified Black male patients.[34] However, this study analysis showed no statistical interaction between genomic ancestry and DCM-related rare variant group, indicating that the propensity to have a P/LP variant with advanced disease was independent of African or European ancestry.

Despite genetic data shown here to inform the diagnostic yield of genetic testing among patients referred to advanced therapies programs in the United States, and to trigger genetic testing for at-risk relatives, this study was not designed to test whether genetic information from specific patients could inform the timing or process of care to improve their outcomes. For example, whereas patients with *LMNA*-associated DCM have been shown to have a worse outcome trajectory compared with other genetic causes,[10] the use of *LMNA* genetic information has not yet been shown to have usefulness for the triage or care of patients with DCM who may need advanced therapies. This idea may be considered aspirational for advanced DCM: that genetic data can inform the care, timing, or triage to achieve better outcomes for patients

being considered for advanced therapies. Such a prospective study, designed to demonstrate improved outcomes leveraging genetic information, is needed if human genetics information is to be implemented routinely into care pathways at DCM advanced therapies programs.

No difference was observed in the frequency of P/LP variants identified in the ICD and no ICD or LVAD/HT group, even though the ICD group clinical data suggested a greater burden of disease. An explanation for this observation is not clear from this analysis, but again underscores the value of a genetic evaluation for individuals with DCM regardless of severity. The overall sensitivity of genetic testing, historically cited at 35% to 40%, was only 18.6% overall, attributable in part to fewer P/LP variants identified in probands of African ancestry, but also in part because of the more stringent variant adjudication approach used here on the basis of the American College of Medical Genetics[22] and ClinGen-based criteria tailored to DCM,[20] as noted previously. Nevertheless, the approach used here provided results similar to others conducting recent DCM genetic studies.[35]

This study has both strengths and limitations. Strengths include multicenter involvement at geographically widely dispersed clinical sites, with data collected using standardized forms and systematic approaches, and with inclusion of a large number of individuals of ancestry besides European. Study limitations include the cross-sectional nature of the study, with only a one-point-in-time opportunity to observe relevant cardiovascular phenotypes, meaning that this study could only demonstrate an association rather than a causal relationship between DCM-related rare variants and DCM severity. Whereas other DCM outcome studies have shown that patients with DCM who carry P/LP variants in DCM-relevant genes have a worse outcome than those without such variants,[10] a prospective, longitudinal study would be needed to confirm similar results in this study, although the results presented here are congruent with such outcomes. Another limitation is lack of robust data regarding ICD treatment of symptomatic arrhythmias; nevertheless, sudden cardiac death was recorded and occurred relatively infrequently in the 3 groups of interest. Because the study patients are from advanced heart failure clinics, the results may not be generalizable to all patients with DCM. Notwithstanding these limitations, this study has provided new information on the diagnostic yield of genetic testing in patients with advanced DCM, defined as having had a durable LVAD/HT, who were more than twice as likely to carry a DCM gene variant classified as P/LP compared with patients with DCM without advanced disease, a finding observed in patients with DCM of either African or European ancestry.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S3

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