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Rare variant genetics and dilated cardiomyopathy severity: The DCM Precision Medicine Study

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None.

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Abstract

Background—Dilated cardiomyopathy (DCM) may lead to advanced disease, defined herein as a patient having received a durable left ventricular assist device (LVAD) or a heart transplant (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, who were a geographically diverse, multi-racial/ethnic cohort. Clinical evaluation included standardized patient interview and medical record query forms. DCM severity was classified into 3 groups: 1) patients with advanced disease who had received a durable LVAD or HT, 2) patients with an implantable cardioverter defibrillator (ICD) only, or 3) patients with no ICD, LVAD or HT. Rare variants in 36 DCM genes were classified as pathogenic, likely pathogenic or variants of uncertain significance (P, LP, VUS). Confounding factors considered included demographics, 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% of European ancestry, and 44% female. Of 1,198 patients, 347 had LVAD/HT, 511 had an ICD, and 340 had no LVAD/HT or ICD. The percentage of patients with P/LP variants was 26.2%, 15.9%, and 15.0% for those with LVAD/HT, with ICD only, and for those with neither, respectively. After controlling for social-demographics and comorbidities, DCM patients with LVAD/HT were more likely than those without LVAD/HT or ICD to have DCM-related P/LP rare variants (OR=2.3,

95% CI: 1.5-3.6). The association did not differ by ancestry. Rare variant genetic findings were similar between DCM patients with an ICD and those without LVAD/HT or ICD.

Conclusion—Advanced DCM was associated with higher odds of rare variants in DCM genes adjudicated as P/LP, compared with those 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.

Keywords

dilated cardiomyopathy; genetics

INTRODUCTION

Risk predictors for DCM outcomes remain difficult to personalize for patients and their families because of the heterogeneity of DCM presentation,[1] and especially for advanced disease defined herein as requiring a durable left ventricular assist device (LVAD) or a heart transplant (HT). Although patients with familial dilated cardiomyopathy may present at earlier age,[2] the rare variant genetics associated with advanced disease from dilated cardiomyopathy (DCM) has remained less studied. Of four case series of patients with advanced DCM and genetic sequence analysis, one reported 30 patients,[3] most having had a left ventricular assist device or a heart transplant, with 51% having a pathogenic variant considered to explain their disease. In three additional case series, all with patients who had undergone cardiac transplantation, one included 52 familial DCM patients with a yield of 40% pathogenic variants.[4] Another study reported 13 patients of whom 8 had familial DCM, with a yield of one likely pathogenic *LMNA* variant.[5] Another study reported 10 of 26 (38%) DCM patients 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 based on 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 DCM patients.[8] Moreover, most had no information regarding race or ethnicity,[2, 3, 7, 8, 10–12] or if information regarding race was provided[9] by very few non-White participants.

DCM that leads to the need for LVAD or 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 impact of self-determined race on DCM outcomes has been suggested to be relevant. Specifically, 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 above 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 who were a geographically representative, multi-racial and ethnic 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 DCM patients with LVAD or HT, with implantable cardioverter-defibrillator (ICD) only, or none (no ICD, LVAD or HT), while controlling for other influential factors related to patient outcomes.

METHODS

The data from this paper are available at dbGaP 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/heart transplant cardiologists and clinical research personnel in heart failure and heart transplant programs at multiple sites in the DCM Consortium from across the U.S.[13] The Institutional Review Boards (IRB) at the Ohio State University and all clinical sites approved the initial study, followed by single IRB oversight at the University of Pennsylvania. All participants gave written informed consent. This analysis used the data from all eligible patients with DCM aged 15 years and older (n=1198) (Figure 1). Study inclusion and exclusion criteria have been previously reported.[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 (LVSD) defined by a left ventricular ejection fraction (LVEF) <50%, and left ventricular enlargement (LVE) defined by a left ventricular internal diastolic dimension >95%th percentile for height and sex[18], with other usually detectable clinical causes excluded, as previously defined.[13, 16] Available cardiac magnetic resonance imaging data were used to validate the study's DCM phenotype and exclude other clinically identifiable etiologies.[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: 1) those with advanced DCM, defined as those who had received a durable LVAD or HT; 2) those who had an ICD, and 3) those who did not have a LVAD, HT or ICD. The latter two groups were collectively defined as not having advanced DCM. The ICD group was selected as the presence or absence of an ICD could be conclusively determined, and most DCM patients in the US with ICDs

compared to those with no ICD represented patients with 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 (ACMG)[22] and ClinGen-based criteria tailored to DCM[20] and assigned to an ACMG category: pathogenic (P), likely pathogenic (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 social demographic (e.g., 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 based on the date at DCM diagnosis and date at LVAD or HT (whichever came first) for patients with LVAD/HT, whereas for patients with ICD only or neither, the DCM duration was based on 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] for the collection, analysis, presentation and discussion of race, ethnicity and ancestry and has adopted recommended approaches.[24–27] This study examined if 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 due to small numbers (n=4).

Self-reported race and ethnicity data were also included in this study because of their relevance for health outcomes; they 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 three DCM severity groups were compared by subgroups of social-demographics and clinical characteristics with means and standard deviations if normally distributed, or median 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, 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. Based on the literature review, confounding factors considered included any factors, other than genetic findings, that may associate with DCM occurrence and outcomes, including social demographic variables (e.g., sex, ancestry, education, and tobacco use), health care access and care quality (e.g., health insurance coverage and geographic region of study sites), DCM duration, and comorbidities. We did not control for age at diagnosis as it is known to be associated with genetic susceptibility, and including it in the model may adjust the genetic effect away.

Three statistical models were developed to assess the associations between DCM severity (LVAD/HT and 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% CI were estimated based on multinomial models with generalized logit link. The interaction between presence of DCM-related rare variant group and genomic ancestry (African ancestry vs. European ancestry) were examined in the 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% of European ancestry, and 44% female; high correlation was noted with self-identified race with 43.0% Black patients and 56.8% White patients (Table 1). Of 1,198 patients, 347 (29.0%) had LVAD or 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 VAD/TX had a biventricular pacemaker. Overall, 223 (18.6%) patients harbored P/LP variants in high evidence DCM-associated genes, and 515 (43.0%) harbored VUSs only with minimal difference by age (Tables S1, S3).

Table 1 presents social demographic and clinical characteristics of patients with DCM for the three DCM severity groups. DCM patients with LVAD/HT tended to be younger at diagnosis and were more likely to be male, self-reported as Hispanic or Black or be classified with African ancestry, to have had 12 or fewer years of education, and to reside

in the South and West compared with those with an ICD or no LVAD/HT/ICD. DCM patients with LVAD/HT also had higher LVIDDs 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%) and sudden cardiac death (7.6% versus 0.6%). The no LVAD/HT/ICD group also had overall milder disease compared to the ICD group, with shorter duration of disease, less LVE, a higher LVEF, and less history of heart failure. The history of arrhythmias/conduction system disease, or history of sudden cardiac death, both suggest milder disease in the group with no ICD/LVAD/Transplant.

Table 2 and Figure 2 presents 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 three DCM severity groups, the percent with P/LP variants was lower in African ancestry patients than in European ancestry patients. The list of variants was 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 (OR=1.9, 95% CI=1.2-2.8) (Model 1). After the adjustment for socio-demographic 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 and European ancestry (P for 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 DCM patients, those who had advanced DCM, defined as having had a LVAD or HT, were more than twice as likely to carry a rare variant in a DCM gene classified as pathogenic or likely pathogenic compared to DCM patients without advanced disease. This finding was observed in DCM patients of both African and European ancestry, after controlling for the effects of socio-demographic factors, 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 importantly inclusive of patients of African ancestry.

Clinical relevance of these findings is also amplified when considering the opportunity to prevent DCM in the at-risk family members of patients with advanced DCM, as greater than 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 such guidelines would include the routine genetic testing of DCM patients 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 DCM patients 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 based upon 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 of DCM has a genetic basis. Also, due to a randomized study for the return of genetic results,[17] most patients enrolled had not had prior 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, because at diagnosis the disease trajectory of DCM is unpredictable, and no single clinical measure or biomarker can summarize overall risk. Though 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, while others will show minimal favorable responses.[7–9, 12] Ultimately one of three outcomes eventuate: 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 one of three categories, those who had received advanced therapies defined as heart transplant or LVAD, those who had received an ICD, or those who had received none of those interventions. The ICD classification was selected because 1) the presence or absence of an ICD could be unambiguously identified; 2) in the US DCM patients who are provided ICDs for primary prevention are required to have sustained left ventricular dysfunction with a LV ejection fraction <35% for several months following the institution of medical therapy,[31] suggesting that such a cohort may have had more advanced disease than DCM patients who had not received an ICD; and 3) 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/LVAD/transplant group were clinically distinctive from one another, as the no ICD/LVAD/transplant group as noted above 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 based on medical criteria could have been precluded from such treatment based on non-medical 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 he diagnostic yield of genetic testing among patients referred to advanced therapies programs in the US, and as well to trigger genetic testing for at-risk relatives, both laudable outcomes, 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, while patients with *LMNA*-associated DCM have been shown to have a worse outcome trajectory compared to other genetic causes,[10] the use of *LMNA* genetic information has not yet been shown to have utility for the triage or care of patients with DCM who may need advanced therapies. This idea may be considered fully aspirational for advanced DCM: that genetic data can usefully 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 sorely needed if human genetics information is to be routinely implemented 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/LVAD/transplant 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. We also note that the overall sensitivity of genetic testing, historically cited at 35-40%, was only 18.6% overall, due in part to fewer P/LP variants identified in probands of African ancestry, but also in part due to the more stringent variant adjudication approach used here based on the ACMG[22] and ClinGen-based criteria tailored to DCM[20] as noted above. 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 multi-center involvement at geographically widely dispersed clinical sites, with data collected using standardized forms and systematic approaches and, importantly, 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. While 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 three groups of interest. Lastly, as the study patients are from advanced heart failure clinics, the results may not be generalizable to all DCM patients.

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 or HT, who were more than twice as likely to carry a DCM gene variant classified as pathogenic or likely pathogenic compared to DCM patients without advanced disease, a finding observed in DCM patients of both African and European ancestry.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Non-standard Abbreviations and Acronyms.

LVAD	left ventricular assist device
HT	heart transplant
ICD	implantable cardioverter-defibrillator
P	pathogenic
LP	likely pathogenic
VUS	variant of uncertain significance

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Clinical Perspective

What is New?

- This multisite study of patients with dilated cardiomyopathy compared three DCM severity groups (having had a LVAD or HT, having an ICD only, or having no LVAD/HT/ICD) and found that patients with LVAD or HT were more than twice as likely to carry a rare variant in a DCM gene classified as pathogenic or likely pathogenic compared to DCM patients without LVAD/HT.
- The study was the first that recruited a large number of DCM patients 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 as more than 1 in 4 patients with advanced disease had actionable genetic findings and providing compelling indications for genetic testing of their first-degree relatives (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 the disease management and outcome assessment, which applies to patients of African ancestry as well as patients of European ancestry.

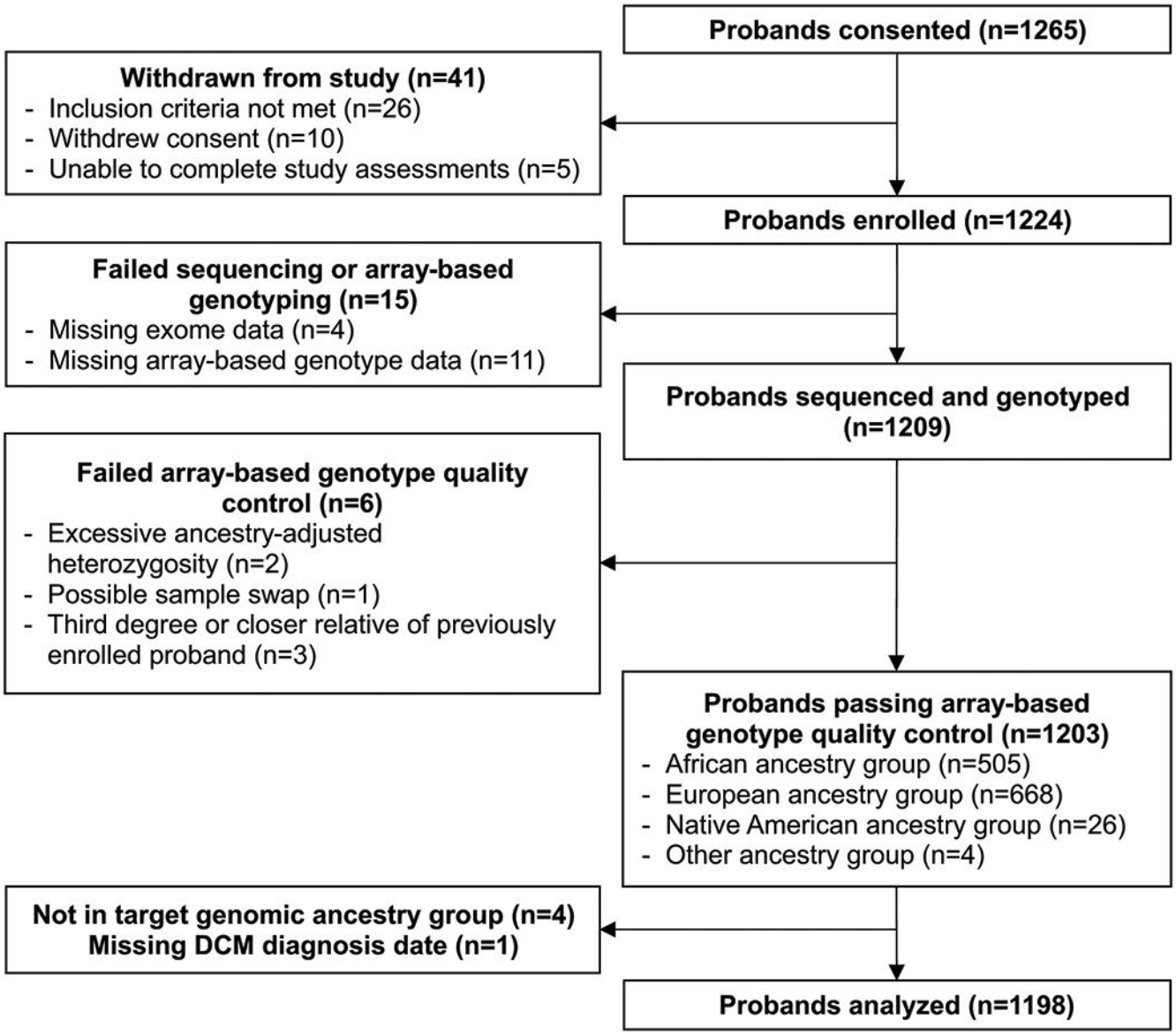
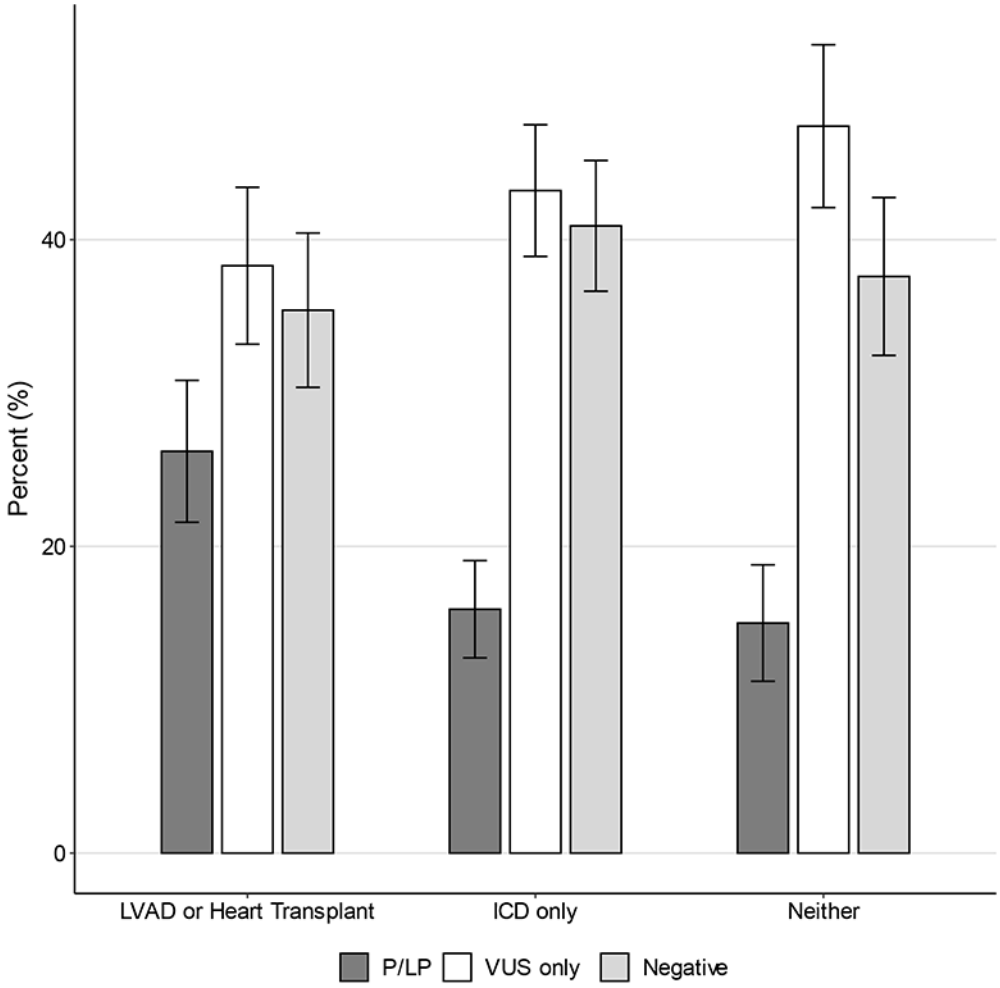


Figure 1.
DCM Precision Medicine Study recruitment and analysis.



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.

This figure presents the percent distributions of patients by their most deleterious DCM-related rare variant (P/LP, VUS only, or negative) and DCM severity status (LVAD/HT, ICD only, or neither). The percentage of patients with P/LP variants was higher for those with LVAD/HT compared with those with ICD and none (26.2%, 15.9%, and 15.0%, respectively, Ps<0.001). Abbreviations: ICD=Implantable cardioverter-defibrillator.

LVAD=Left ventricular assist device. P/LP=Pathogenic/Likely pathogenic. VUS=Variant of uncertain significance.

Table 1.

Demographic and clinical characteristics of patients with dilated cardiomyopathy by DCM severity (with durable left ventricular support device or heart transplant, with ICD only, or none).

Variable	With LVAD or Heart Transplant	With ICD	Neither	Total
Total number	347 (100.0)	511 (100.0)	340 (100.0)	1198 (100.0)
Age at diagnosis, mean (SD)	41.5(12.9)	45.5 (13.1)	44.9 (14.4)	44.2 (13.5)
Age at enrollment, mean (SD)	51.6 (13.4)	53.5 (13.0)	49.8 (14.3)	51.9 (13.6)
Female, n (%)	120 (34.6)	237 (46.4)	167 (49.1)	524 (43.7)
Self-reported race/ethnicity, n (%)				
Hispanic	31 (8.9)	44 (8.6)	27 (7.9)	102 (8.5)
Race				
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, n (%)				
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, n (%)				
<=12 yrs	147 (44.7)	194 (40.6)	104 (32.6)	445 (39.5)
>12 yrs	182 (55.3)	284 (59.4)	215 (67.4)	681 (60.5)
Missing	18	33	21	72
US region of study site, n (%)				
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				
<5 years	167 (48.3)	235 (46.0)	239 (70.3)	641 (53.6)
>=5 years	179 (51.7)	276 (54.0)	101 (29.7)	556 (46.4)
Missing	1	0	0	1
Echo findings[1]				
LVIDD, mm, mean (SD)	68.6 (8.6)	65.6 (8.0)	62.6 (6.8)	65.6 (8.2)
LVIDD z score[2], mean (SD)	4.8 (1.9)	4.4 (1.7)	3.8 (1.4)	4.3 (1.7)
LVEF, median (IQR)	20.0 (8.0)	20 (15.0)	25.0 (14.5)	20.0 (14.0)
ECG findings, n (%)				
Atrial fibrillation	25 (7.3)	29 (5.7)	18 (5.3)	72 (6.0)
1st degree AV block	30 (8.7)	34 (6.7)	13 (3.8)	77 (6.5)
2nd degree AV block	1 (0.3)	0	0	1 (0.1)

Variable	With LVAD or Heart Transplant	With ICD	Neither	Total
3rd 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, n (%)				
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, n (%)				
Heart failure	344 (99.1)	440 (86.1)	269 (79.1)	1,053 (87.9)
Arrhythmias/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)
Tobacco use (ever), Yes, n (%)	144 (41.7)	204 (40.0)	132 (38.9)	480 (40.2)
Missing	2	1	1	4
Health insurance coverage, yes, n (%)	313 (92.9)	428 (86.1)	297 (90.0)	1,038 (89.2)
Missing	10	14	10	34

Abbreviations: ICD = Implantable cardioverter-defibrillator. LVAD = Left ventricular assist device. LVIDD = Left ventricular internal diastolic dimension. LVEF = Left ventricular ejection fraction.

*1170 LVIDD and 1172 LVEF are from Echo, while 22 LVIDD and 21 LVEF are from CMR.

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

Table 2.

Most deleterious DCM-related rare variant (P, LP, and VUS) found in patients with idiopathic cardiomyopathy, by DCM severity (LVAD/HT, ICD, or none)

Presence of DCM-related rare variants	Total	LVAD or heart transplant (N=347) n (%)	With ICD (N=511) n (%)	Neither (N=340) n (%)	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)	

Abbreviations: ICD=Implantable cardioverter-defibrillator. LVAD=Left ventricular assist device. P/LP=Pathogenic/Likely pathogenic. VUS=Variant of uncertain significance.

*P value is based on the Chi-Square test that compares distributions of the DCM-related variant group by the three DCM severity group.

Table 3.

Association of DCM severity with the most deleterious DCM-related rare variant found.

Presence of DCM-related rare variants	**LVAD or heart transplant vs. Neither OR (95% CI)**	**With ICD vs. 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 [1]. 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 [2]. 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

Abbreviations: ICD=Implantable cardioverter-defibrillator. LVAD=Left ventricular assist device. P/LP=Pathogenic/Likely pathogenic. VUS=Variant of uncertain significance.

Note: Estimates are based on multinomial models with generalized logit link. Response variable is unordered and “Neither” ((i.e., with no LVAD, heart transplant or ICD)) is the reference group.

[1]Model 2 controlled for genomic ancestry (AA, EA, or NA), 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 ORs for the DCM-related rare variant groups.

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