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ORIGINAL INVESTIGATIONS

Screening for Dilated Cardiomyopathy in At-Risk First-Degree Relatives

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on behalf of the DCM Precision Medicine Study of the DCM Consortium

ABSTRACT

BACKGROUND Cardiovascular screening is recommended for first-degree relatives (FDRs) of patients with dilated cardiomyopathy (DCM), but the yield of FDR screening is uncertain for DCM patients without known familial DCM, for non-White FDRs, or for DCM partial phenotypes of left ventricular enlargement (LVE) or left ventricular systolic dysfunction (LVSD).

OBJECTIVES This study examined the yield of clinical screening among reportedly unaffected FDRs of DCM patients.

METHODS Adult FDRs of DCM patients at 25 sites completed screening echocardiograms and ECGs. Mixed models accounting for site heterogeneity and intrafamilial correlation were used to compare screen-based percentages of DCM, LVSD, or LVE by FDR demographics, cardiovascular risk factors, and proband genetics results.

RESULTS A total of 1,365 FDRs were included, with a mean age of 44.8 ± 16.9 years, 27.5% non-Hispanic Black, 9.8% Hispanic, and 61.7% women. Among screened FDRs, 14.1% had new diagnoses of DCM (2.1%), LVSD (3.6%), or LVE (8.4%). The percentage of FDRs with new diagnoses was higher for those aged 45 to 64 years than 18 to 44 years. The age-adjusted percentage of any finding was higher among FDRs with hypertension and obesity but did not differ statistically by race and ethnicity (16.2% for Hispanic, 15.2% for non-Hispanic Black, and 13.1% for non-Hispanic White) or sex (14.6% for women and 12.8% for men). FDRs whose probands carried clinically reportable variants were more likely to be identified with DCM.

CONCLUSIONS Cardiovascular screening identified new DCM-related findings among 1 in 7 reportedly unaffected FDRs regardless of race and ethnicity, underscoring the value of clinical screening in all FDRs.
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ABBREVIATIONS AND ACRONYMS

DCM = dilated cardiomyopathy

ECG = electrocardiogram

FDR = first-degree relative

LVE = left ventricular enlargement

LVSD = left ventricular systolic dysfunction

P/LP = pathogenic/likely pathogenic

VUS = variant(s) of uncertain significance

Idiopathic dilated cardiomyopathy (DCM) is a heritable disease with age-related penetrance.[1] The risk of a family member developing DCM or a DCM partial phenotype by age 80 years has been estimated to be 33%,[2] with partial phenotype defined as left ventricular enlargement (LVE) only or left ventricular systolic dysfunction (LVSD) only. With a new DCM diagnosis, guidelines recommend a family-based genetic evaluation of first-degree relatives (FDRs), including the use of clinical cardiovascular screening and genetic testing as indicated, to mitigate shared risk for DCM in families.[1,3-5] Clinical cardiovascular screening, here meaning a cardiovascular history, examination, electrocardiogram (ECG), and cardiac imaging, accomplishes 2 purposes. The first is to identify the earliest possible evidence of cardiomyopathy in FDRs of DCM patients, including asymptomatic DCM or a DCM partial phenotype.[2] This enables personalized surveillance or therapeutic intervention before the onset of symptoms with the goal to prevent advanced DCM or premature sudden death.

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Although detecting presymptomatic DCM in at-risk family members has a compelling rationale, the second purpose of clinical screening is to provide data to enhance the clinical translation of genetic information into family-based care. Genetic testing of DCM-relevant genes identifies pathogenic (P) or likely pathogenic (LP) variants in less than one-quarter of DCM cases, while nearly 50% of probands are found to carry variants of uncertain significance (VUS).[6] Because only P or LP variants are useful for predictive testing, additional clinical data from FDRs may enhance interpretation of VUS, which at times can help elevate VUS to P/LP classification.

Most recommendations for family-based screening after a DCM diagnosis have been based on single-center studies at academic referral centers that have emphasized familial and genetic DCM, had relatively small sample sizes, and lacked racial or ethnic diversity. Most have not evaluated the DCM partial phenotypes of LVE or LVSD as harbingers of DCM. Also, it has been unclear if the yield of clinical cardiovascular screening to detect a full or partial DCM phenotype among reportedly unaffected, at-risk family members differs by demographics, race and ethnicity, and cardiovascular risk factors. Conventional preventable or modifiable clinical risk factors, such as obesity, hypertension, smoking, and diabetes, are associated with progression of cardiovascular disease. Substance use (eg, alcohol, cocaine) also has been found to be associated with risk of DCM.[7,8]

The DCM Precision Medicine Study, conducted by 25 clinical sites of the DCM Consortium, recruited nearly 1,800 FDRs of DCM patients (probands) between 2016 and 2021, emphasizing enrollment of Black and Hispanic probands.[2] The general hypothesis of the DCM Precision Medicine Study was that most DCM, whether familial or nonfamilial, had a substantial genetic basis. Accordingly, although DCM patients with known familial disease were eligible for inclusion, enrollment of patients without known familial DCM was prioritized by investigators. Thus, data from the DCM Precision Medicine Study provided a unique opportunity to evaluate the diagnostic yield of family screening for early identification of DCM among reportedly unaffected FDRs of patients with DCM by race/ethnicity, demographic and cardiovascular risk factors, and probands' genetic results, which closely simulates the situation encountered by most clinicians in everyday practice.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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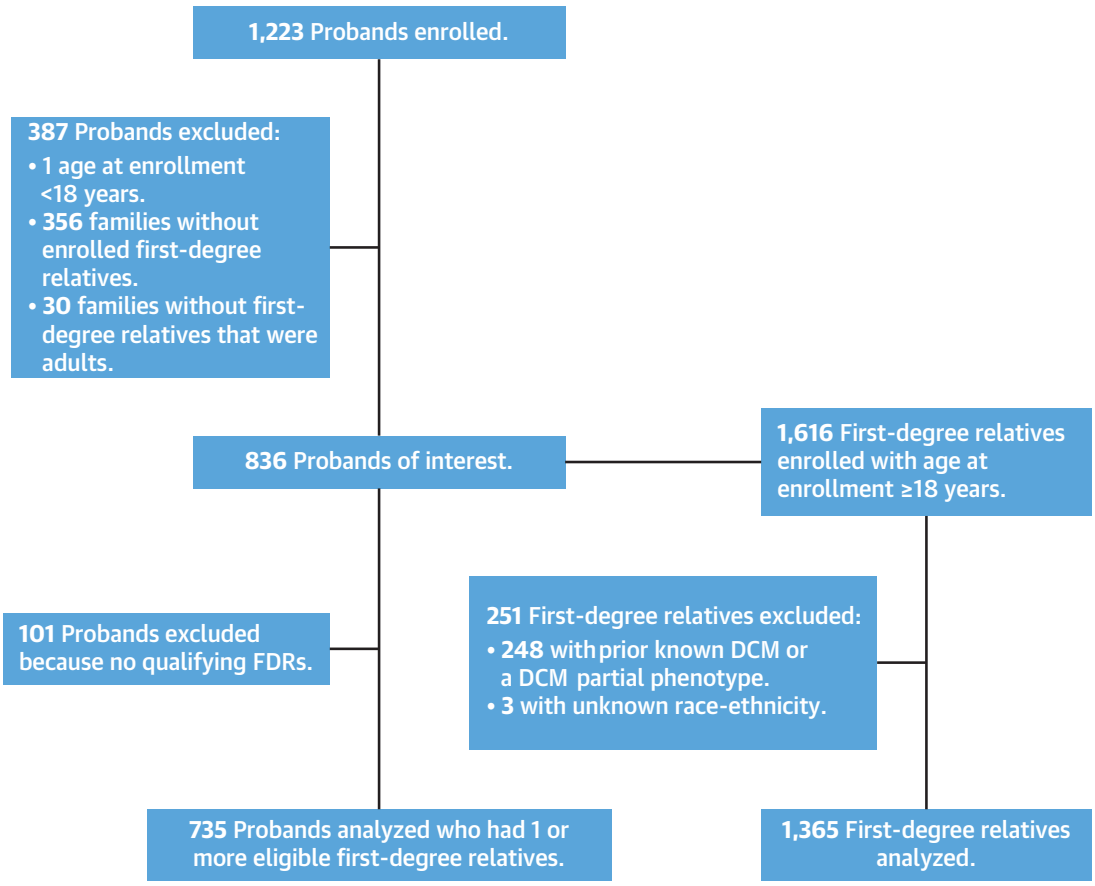
FIGURE 1 Flow Chart of Screened First-Degree Relatives



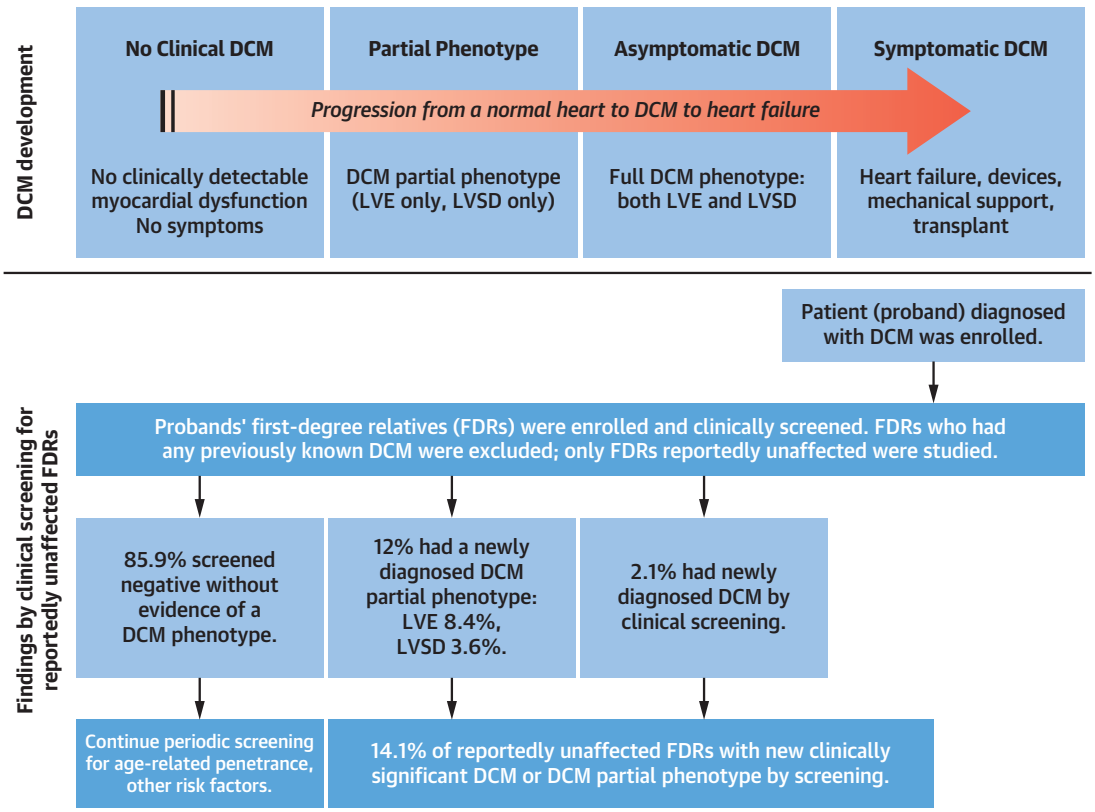
Information on inclusion and exclusion for the Precision Medicine dilated cardiomyopathy (DCM) study and this analysis. The **left boxes** describe the enrollment and selection of eligible probands. The **right boxes** describe the enrollment and selection of eligible first-degree relative (FDR) for the analysis.

METHODS

THE DCM PRECISION MEDICINE STUDY. This analysis was based on baseline data from the DCM Precision Medicine Study.[2,9] The study aims, design, and data collection process and procedures of the study were described previously.[2,6,9] Briefly, the study enrolled 1,223 probands with DCM and 1,781 of their FDRs. Study inclusion and exclusion criteria were previously reported.[2,9] 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 focused on FDRs of adult probands. Eligible FDRs were those aged 18 years and older who were asymptomatic and not known to have DCM at the time of enrollment (**Figure 1, Central Illustration**). Of the 1,223 probands enrolled in the DCM Precision Medicine Study, 836 were adults who had 1 or more adult FDR enrolled. Of those 836 probands, 101 had no eligible FDRs for this analysis, and thus were excluded, leaving 735 DCM probands for analysis who had 1 or more enrolled FDR not previously known to have a DCM phenotype at the time of enrollment. All FDRs with DCM or DCM partial phenotypes that were known at the time of study enrollment were removed from this analysis, leaving 1,365 FDRs for analysis.

CENTRAL ILLUSTRATION **Clinical Screening of Reportedly Unaffected First-Degree Relatives of Patients With Dilated Cardiomyopathy**



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(Top) The progression from a normal heart to dilated cardiomyopathy (DCM) occurs over years. In this progression, a DCM partial phenotype, left ventricular enlargement (LVE), or left ventricular systolic dysfunction (LVSD), is observed before the development of a full asymptomatic DCM phenotype, which eventually presents with symptoms. **(Bottom)** Probands with DCM had relatives screened according to clinical guidelines and the study protocol. Of enrolled relatives reported to be unaffected, 14.1% had new DCM, LVE, or LVSD detected. Of those with negative screening, surveillance has been recommended to continue at age-defined intervals. Other factors, such as additional genetic variation or lifestyle, may affect disease presentation over time.

CARDIOVASCULAR SCREENING FOR DCM AND DCM PARTIAL PHENOTYPES. All probands met diagnostic criteria for DCM, which included LVSD defined by a left ventricular ejection fraction <50% and LVE defined by a left ventricular internal diastolic dimension >95th percentile for age and sex,[10] with other usual clinical causes excluded, as previously defined.[2,9] Available CMR data were used to retrospectively validate the study's DCM phenotype.[11] FDRs who had either LVSD or LVE, but not both, without known cause were referred to as having a DCM partial phenotype.[2]

At enrollment probands were asked to inform all living FDRs of the study and to seek their oral permission for contact by study personnel. Study staff then sought enrollment of FDRs who provided oral permission for contact. For most FDRs (88.4% of this FDR cohort), a research-based cardiovascular-directed history and examination, an ECG, and a transthoracic echocardiogram were obtained at a DCM Consortium site. Alternatively, the results of clinical screening accomplished by the FDRs' physician as part of recommended clinical care, if available and within 3 years, could be used (11.8%).

A structured medical record query form was used to abstract cardiovascular medical information for probands and FDRs.

Clinical data from FDRs were centrally adjudicated to establish whether DCM, LVSD, or LVE phenotypes were present. Central adjudication, including ECG interpretation, was performed by The Ohio State University site principal investigator (G.H.). Research echocardiograms were interpreted at sites by study site cardiologists. All clinical data were interpreted without knowledge of family relationships or genetic information.

DEMOGRAPHIC AND CLINICAL INFORMATION COLLECTED. Structured interviews collected participant demographic and health history information; medical record questionnaires summarized key cardiovascular clinical information. Information on hypertension and diabetes was obtained from medical record review. Obesity was defined by body mass index ≥30 kg/m^2 based on weight and height at the time of enrollment. Race and ethnicity were included because of their relevance for health outcomes, and were self-reported by participants using structured race (Native American or Alaska Native, Asian, African American, Native Hawaiian or Pacific Islander, White, >1 race, or unknown) and Hispanic ethnicity (yes, no, or unknown) categories. Global health status and lifestyle risk factors, such as cigarette smoking, alcohol use, amphetamine use, and cocaine use, were measured by a patient interview at enrollment. The geographic location of residence was based on the home address reported by participants. Educational attainment was obtained by asking participants how many years of school they had completed.

GENETIC DATA COLLECTION. Research exome sequencing and array-based genotyping of individuals with DCM diagnoses were conducted at the University of Washington Genome Sciences laboratory, 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. Variants were adjudicated using American College of Medical Genetics[12] and ClinGen-based criteria tailored to DCM[6] and assigned to an American College of Medical Genetics category: pathogenic (P), likely pathogenic (LP), variant of uncertain significance (VUS), likely benign, or benign; P, LP, and VUS were confirmed by Sanger sequencing.

STATISTICAL ANALYSIS. Characteristics of the selected probands and their FDRs were described with mean ± SD if normally distributed, or median (IQR) if not normally distributed. Percentages of FDRs with DCM, LVSD, or LVE were described overall and by demographics (age, sex, and race/ethnicity), lifestyle factors (smoking, alcohol consumption, and use of amphetamine and cocaine), and cardiovascular risk factors (eg, hypertension, diabetes, obesity). Continuous variables were categorized if they were not linearly associated with the outcome.

Because age is a strong predictor for the penetrance of DCM, age-adjusted percentages were obtained for subgroup comparisons. To obtain age-adjusted and unadjusted percentages of DCM, LVSD, or LVE for different subgroups, a generalized estimating-equation type logistic mixed model was fit using residual subject-specific pseudo-likelihood. The models included a random effect for proband enrollment site to account for site heterogeneity; inferences are thus conditional on site. Intrafamilial correlation was accounted for within a generalized estimating-equation framework by using a working independence correlation matrix and the Morel, Bokossa, and Neerchal bias-corrected empirical covariance estimator.[13] The age-adjusted percentage was estimated using the marginal standardization method, in which the predicted probability is a weighted average over the distribution of the enrollment age group.[14] The 95% CIs were obtained using the same method. Wald *P* values for differences in these percentages were obtained using the delta method with a standard normal distribution.

All statistical tests were 2-sided with significance level of 0.05. The Bonferroni correction was used to reduce inflated type I error within multiple comparisons for subgroup analysis. All analyses were performed in R version 4.0.2 (R Foundation for Statistical Computing), and SAS/STAT 15.2 software, version 9.4 (TS1M7) of the SAS System for 64-bit Windows (SAS Institute).

RESULTS

PROBANDS WITH DILATED CARDIOMYOPATHY. Of the 735 probands, nearly one-half were women and one-half had been diagnosed with DCM at ages 18 to 44 years (Table 1). The racial and ethnic distribution was mostly non-Hispanic Black (34.1%) and non-Hispanic White (57.0%). About two-thirds of probands lived in the Midwest and South. Common comorbidities included hypertension, obesity, and diabetes. The percentages of probands who carried a P/LP variant or a VUS only were 19.5% and 42.2%, respectively (Table 1). Frequencies of genetic variants

TABLE 1 Social Demographic Characteristics and Comorbidities of the Study DCM Patients and Their First-Degree Relatives

	Probands[a]	First-Degree Relatives[a]
Total	735 (100.0)	1,365 (100.0)
Age at enrollment, y		
18-44	217 (29.5)	703 (51.5)
45-64	372 (50.6)	464 (34.0)
≥65	146 (19.9)	198 (14.5)
Age at DCM diagnosis, y		
<45	368 (50.1)	NA
45-64	312 (42.4)	NA
≥65	55 (7.5)	NA
Race/ethnicity		
Hispanic	65 (8.8)	134 (9.8)
Non-Hispanic Black	251 (34.1)	376 (27.5)
Non-Hispanic White	419 (57.0)	839 (61.5)
Non-Hispanic Other	0 (0.0)	16 (1.2)
Sex		
Women	337 (45.9)	842 (61.7)
Men	398 (54.1)	523 (38.3)
Education		
≤12 y	262 (37.5)	468 (35.7)
>12 y	436 (62.5)	844 (64.3)
Missing	37	53
Residential region[b]		
Northeast	91 (12.4)	152 (11.2)
Midwest	254 (34.6)	502 (36.9)
South	286 (38.9)	471 (34.6)
West	104 (14.1)	237 (17.4)
Hypertension		
Yes	371 (50.5)	354 (25.9)
No	364 (49.5)	1,011 (74.1)
Obesity (BMI ≥30 kg/m^2)		
Yes	343 (46.7)	607 (44.6)
No	392 (53.3)	753 (55.4)
Missing	0	5
Diabetes		
Yes	184 (25.0)	90 (6.6)
No	551 (75.0)	1,275 (93.4)
Tobacco use (ever)		
Yes	289 (39.3)	395 (29.1)
No	446 (60.7)	962 (70.9)
Missing	0	8
Years smoked	16.0 ± 11.8	14.6 ± 12.0
Missing	14	21
Cigarettes/d	15.1 ± 13.9	11.3 ± 10.3
Missing	22	30
Alcohol use (ever) and consume ≥5 drinks in an occasion		
Yes	60 (8.2)	96 (7.1)
No	670 (91.8)	1,255 (92.9)
Missing	5	14
Alcohol use frequency		
1-3 times/mo or <1 time/mo	219 (43.7)	443 (46.0)
1-3 times/wk	188 (37.5)	376 (39.1)
4-7 times/wk	94 (18.8)	143 (14.9)
Missing	4	6
Amphetamine use (ever)		
Yes	39 (5.3)	50 (3.7)
No	696 (94.7)	1,307 (96.3)
Missing	0	8
Years of amphetamine use	5.8 ± 8.9	5.5 ± 6.1
Missing	7	5
Amphetamine use frequency		
1-3 times or <1/mo	8 (25.0)	14 (30.4)
1-3 times/wk	4 (12.5)	3 (6.5)
4-7 times/wk	20 (62.5)	29 (63.0)
Missing	7	4
Cocaine use (ever)		
Yes	50 (6.8)	51 (3.8)
No	685 (93.2)	1,306 (96.2)
Missing	0	8
Cocaine use frequency		
1-3 times/mo or <1 time/mo	27 (56.2)	34 (69.4)
1-3 times/wk	13 (27.1)	5 (10.2)
4-7 times/wk	8 (16.7)	10 (20.4)
Missing	2	2
Years of cocaine use	6.0 ± 6.3	5.8 ± 8.3
Missing	6	6
Global health status		
Excellent/very good	147 (20.4)	673 (50.3)
Good	251 (34.9)	472 (35.3)
Fair	230 (32.0)	178 (13.3)
Poor	91 (12.7)	14 (1.0)
Missing	16	28
Probands' most deleterious DCM-related rare variants		
P/LP	143 (19.5)	287 (21.1)
VUS	309 (42.2)	556 (40.9)
Negative	280 (38.3)	517 (38.0)
Missing	3	5

Values are n (%), n, or mean ± SD. [a]Percentages may not sum to 100 because of rounding. [b]Excluded 3 first-degree relatives who resided outside of the United States.

BMI = body mass index; DCM = dilated cardiomyopathy; LP = likely pathogenic; P = pathogenic; VUS = variant of uncertain significance.

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(P/LP and VUS) found in specific genes are presented in Supplemental Table 1. The median left ventricular ejection fraction was 20.0% (IQR: 14.4%); the mean left ventricular internal diastolic dimension was 65.6 ± 8.3 mm.

FIRST-DEGREE RELATIVES OF PROBANDS. For the 735 DCM probands included in this analysis, 1,365 enrolled FDRs had no known history of DCM, LVE, or LVSD before study enrollment (Table 1). These FDRs self-identified as Hispanic (9.8%), non-Hispanic Black (27.5%), non-Hispanic White (61.5%), and non-Hispanic of other races (1.2%) (Table 1). Compared with probands, FDRs tended to be younger; were more likely to be women; were less likely to use

TABLE 2 Clinical Characteristics of First-Degree Relatives With Screening-Based DCM or LVE or LVSD

	DCM (n = 29)	LVE (n = 115)	LVSD (n = 49)
Age at diagnosis, y	48.5 ± 15.0	47.4 ± 16.0	43.5 ± 18.0
Echocardiographic findings			
LVIDD, mm	58.5 ± 5.8	55.1 ± 3.4	49.1 ± 5.0
LVIDD (z-score)[a]	2.9 ± 1.1	2.4 ± 0.7	−0.2 ± 1.3
LVEF, %	39.5 [11.2]	57.5 [8.0]	45.0 [4.8]
ECG findings			
Atrial fibrillation	1 (3.4)	1 (0.9)	1 (2.0)
First-degree AV block	1 (3.4)	1 (0.9)	2 (4.1)
Second-degree AV block	0 (0.0)	0 (0.0)	0 (0.0)
Third-degree AV block	0 (0.0)	0 (0.0)	0 (0.0)
LBBB	2 (6.9)	0 (0.0)	1 (2.0)
RBBB	0 (0.0)	1 (0.9)	1 (2.0)
Inferior MI pattern	0 (0.0)	1 (0.9)	1 (2.0)
Anterior MI pattern	0 (0.0)	2 (1.7)	1 (2.0)
Septal MI pattern	0 (0.0)	0 (0.0)	0 (0.0)

Echocardiographic findings are mean ± SD or median [IQR]. ECG findings are n (%). [a]Calculated based on sex and height for all study participants with heights of at least 152 cm (men) or 137 cm (women).

DCM = dilated cardiomyopathy; LBBB = left bundle branch block; LVE = left ventricular enlargement; LVEF = left ventricular ejection fraction; LVIDD = left ventricular internal diastolic dimension; LVSD = left ventricular systolic dysfunction; RBBB = right bundle branch block.

cigarettes, amphetamines, or cocaine; and were less likely to have hypertension, diabetes, or obesity. The majority of FDRs (85.5%) were younger than age 65 years. Residential region and educational attainment were similar between probands and enrolled FDRs.

Of the 1,365 FDRs, 193 (14.1%) were identified to have DCM or a DCM partial phenotype through study-related cardiovascular screening (29 DCM [2.1%]; 115 LVE only [8.4%], 49 LVSD only [3.6%]) (Table 2, Central Illustration). The median left ventricular ejection fraction was 39.5% for FDRs with DCM, 45.0% for those LVSD only, and 57.5% for those with LVE only. Few abnormal ECG findings, such atrial fibrillation, atrioventricular block, LBBB, or RBBB, were observed for these FDRs. The percentage of FDRs with DCM at cardiovascular screening was higher for FDRs aged 45 to 64 years (3.6%) than for those aged 18 to 44 years (1.4%) (difference = 2.2%; 95% CI: 0.3%-4.2%) (Figure 2). Although this percentage for FDRs aged 45 to 64 years was also higher than that for those 65 years and older (1.0%), the difference did not reach statistical significance (difference = 2.6%; 95% CI: −0.5% to 5.7%).

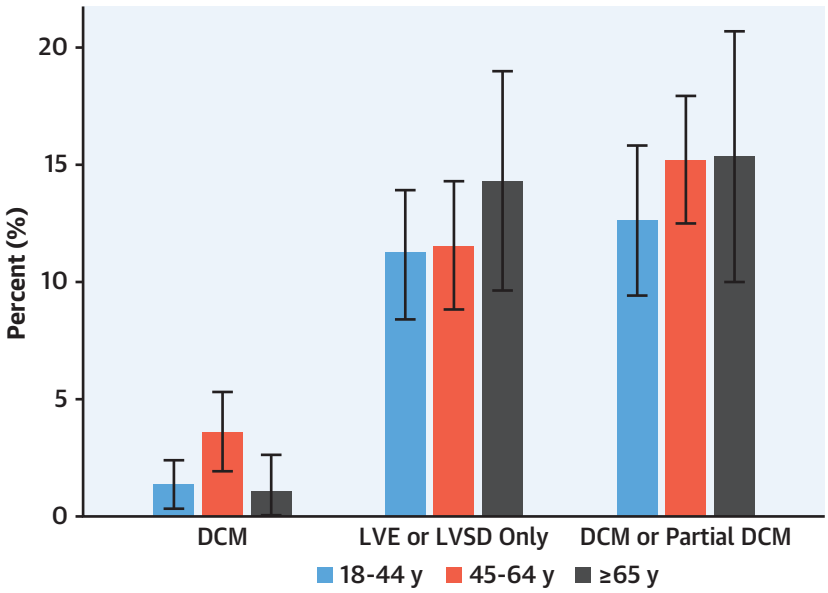
In this analysis, the age-adjusted and unadjusted percentages with DCM and DCM partial phenotypes did not differ statistically among Hispanic, non-Hispanic Black, and non-Hispanic White FDRs (Table 3). However, the age-adjusted percentages of DCM and DCM partial phenotypes were higher among those FDRs with hypertension (20.0% vs 11.8%, difference = 8.3%; 95% CI: 3.3%-13.3%) and obesity (18.3% vs 10.5%, difference = 7.8%; 95% CI: 4.4%-11.2%) compared with those without (Table 3). After additionally adjusting for hypertension and obesity, differences in the age-adjusted percentage with DCM and DCM partial phenotype among the 3 racial and ethnic groups remained statistically nonsignificant (data not shown). The age-adjusted percentages did not differ statistically by sex, educational attainment, residential region, tobacco use, alcohol use, and drug use.

Based on genetic analysis of rare clinically reportable variants (P/LP/VUS) of 36 DCM genes, the age-adjusted percentage of FDRs with DCM was higher among those FDRs whose probands carried P/LP or VUS-classified variants in a DCM-related gene (3.9% and 2.5%, respectively) than those whose probands did not (0.6%) (differences: 3.5% [95% CI: 0.1%-6.9%] and 1.9% [95% CI: 0.3%-3.5%]) (Figure 3A). Age-adjusted percentages of FDRs with a DCM partial phenotype when their probands carried LP/P or VUS variants were not statistically different from those whose probands were found to carry no DCM genetic variants (Figure 3B). The study identified 3 FDRs with DCM whose probands' genetic analyses were negative (Figure 3A). None of these 3 ever used cocaine or amphetamine, but 1 consumed more than 5 alcohol drinks daily for 30 years.

DISCUSSION

After excluding FDRs known to have DCM, this study revealed that 1 of 7 asymptomatic FDRs of patients with DCM had previously unknown DCM or a DCM partial phenotype, LVSD, or LVE. The percentages did not differ statistically by self-identified race and ethnicity, sex, educational attainment, and residential region. Of the age groups studied, the percentage with newly identified DCM was highest among FDRs aged 45 to 64 years, but percentages of FDRs with partial phenotypes of LVSD or LVE were similar by age. We note that the percentages of previously unknown DCM or partial phenotypes were higher among those with hypertension or obesity compared with those without. FDRs whose probands carried a P/LP or VUS only in a DCM gene were more likely to be identified to have DCM by clinical screening compared with those whose probands had no relevant variants identified. Nevertheless, DCM was identified in FDRs of 3 probands whose genetic testing was negative. Overall, the findings from this study underscore the importance of clinical cardiovascular screening for at-risk FDRs of all patients with DCM.

FIGURE 2 First-Degree Relatives With DCM, LVE, or LVSD According to Age Group



Age at Enrollment	N	DCM Only % (95% CI)	LVE or LVSD Only % (95% CI)	DCM, LVE, or LVSD % (95% CI)
18-44 y	703	1.4 (0.3-2.4)	11.2 (8.4-13.9)	12.6 (9.4-15.8)
45-64 y	464	3.6 (1.9-5.3)	11.5 (8.8-14.3)	15.2 (12.5-17.9)
≥65 y	198	1.0 (0-2.6)	14.3 (9.6-19.0)	15.4 (10.0-20.7)

Blue, red, and gray bars depict percentages of first-degree relatives identified with dilated cardiomyopathy (DCM) and left ventricular enlargement (LVE) or left ventricular systolic dysfunction (LVSD) by clinical screening for the 3 age groups. **Error bars** denote the 95% CI. Estimates were obtained using generalized estimating-equation type logistic mixed models accounting for site heterogeneity and intrafamily correlation. The percentage of those with DCM was higher for first-degree relatives aged 45 to 64 years than for those aged younger than 45 years ($P = 0.02$). Percentages of those with LVE or LVSD only or DCM, LVSD, and LVE combined did not differ by age group. Wald P values for differences in these percentages were obtained using the delta method with a standard normal distribution. All comparisons were adjusted by the Bonferroni correction method.

Earlier smaller DCM family studies have shown that approximately one-third of asymptomatic relatives had echocardiographic abnormalities at the time of clinical screening, approximately 5% had DCM, 16% to 20% had LVE, and 3% to 6% had LVSD.[15-18] As has been shown previously, during follow-up evaluation, LVE[15-17,19] or LVSD[16,18] both independently predicted DCM progression. A more recent study conducted in a Copenhagen University Hospital reported similar results.[20] However, another recent study reported that 31 of 475 (6.5%) family relatives of probands with DCM were diagnosed with DCM following family screening, and none had cardiovascular symptoms at diagnosis.[21] In our study, the percentages of FDRs with asymptomatic LVE or LVSD were 8.4% or 3.6%, respectively, which was in accordance with the previously mentioned reports and similar to community-based studies.[18] However, the overall percentage of FDRs with previously unknown DCM here (2.1%) was lower than those previously reported results. These differences may be attributable to variations in demographic distribution of study populations, study sample size, geographic location, and DCM diagnostic criteria. Also, the earlier studies were conducted at major referral centers known to conduct family-based studies for DCM that may have led to referral bias for familial DCM. In contrast, the DCM Precision Medicine study sought to enroll a DCM proband cohort with broadly based inclusion criteria, and actively encouraged the enrollment of DCM patients without any suggestion of a family history of DCM.

We found a higher risk of DCM and DCM partial phenotypes among FDRs with hypertension and obesity, independent of age effect. These findings were not surprising, because DCM was previously shown to be associated with hypertension among women,[22] and concentric left ventricular hypertrophy, increased left ventricular mass, and hypertension have been associated with the subsequent development of left ventricular dysfunction.[23,24] The role of obesity in DCM has been less clear. Obesity, through a wide array of inter-related biological mechanisms, may become a trigger to the development of DCM in the setting of a genetic predisposition.[24,25] An earlier case-control study reported little association between severe obesity and idiopathic dilated cardiomyopathy.[26] A recent study based on U.S. Birth Certificate data revealed an association between prepregnancy obesity and the risk of peripartum cardiomyopathy.[27]

Findings from this analysis demonstrated that the yield of clinical screening did not differ by race or ethnicity, age, or sex, which supports genetic cardiomyopathy guidelines that have recommended clinical cardiovascular screening of all FDRs at risk for DCM regardless of age, sex, race, or ethnicity, and in conjunction with cascade genetic testing when indicated.[1,3-5] Although this analysis did not identify increased frequency of DCM in FDRs by race or ethnicity, likely because FDRs with previously identified DCM or a partial phenotype were excluded, the larger sample size of our prior study observed a 1.89-fold greater risk of DCM in FDRs of non-Hispanic Black probands than FDRs of non-Hispanic White probands when both previously identified and newly identified FDRs were included.[2] Smaller numbers of Hispanic and non-Hispanic Black FDRs also limited the statistical power when comparing racial and ethnic groups.

Scientific statements and guidelines[1,3-5] have universally recognized the value of clinical cardiovascular screening of FDRs of patients diagnosed with DCM. However, few studies have assessed risk of DCM in FDRs based on whether the proband carries a P, LP, or VUS for numerous relevant DCM genes[28] in a systematic recruitment of DCM patients based on phenotype alone, as was done in this study.[6,9] In this study, probands' carrying LP/P or VUS only was statistically associated with FDR risk for DCM but not for the DCM partial phenotypes (LVE only or LVSD only). These findings are fitting for an age-dependent condition such as DCM, where adult-onset DCM may take years to emerge. These preliminary findings also support the concept that variants rigorously defined as VUS for DCM may predict risk for FDRs, as was previously observed in a smaller pilot study.[29] Additional work will be needed to more carefully define the role, if any, of variants classified as VUS for the care of DCM families.

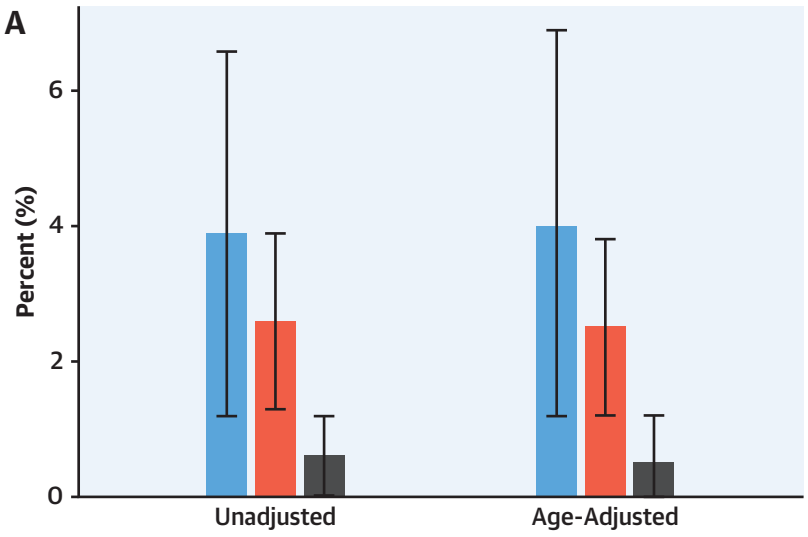
TABLE 3 Age-Adjusted Percentages of First-Degree Relatives Identified With DCM, LVE, or LVSD by Clinical Screening

		Unadjusted[a]		Age-Adjusted[a]	
	n/N	% (95% CI)	*P* Value	% (95% CI)	*P* Value
Sex			0.50		0.52
Women	125/842	14.6 (11.7-17.5)		14.6 (11.6-17.6)	
Men	68/523	12.7 (8.1-17.4)		12.8 (8.0-17.5)	
Race/ethnicity			0.65		0.78
Hispanic	20/134	15.8 (10.1-21.5)		16.2 (9.9-22.5)	
Non-Hispanic Black	60/376	15.1 (11.0-19.1)		15.2 (10.9-19.4)	
Non-Hispanic White	112/839	13.2 (10.5-15.9)		13.1 (10.2-15.9)	
Non-Hispanic other[b]	1/16	5.1 (0-17.7)		5.2 (0-18.7)	
Education			0.75		0.75
≤12 y	68/468	14.4 (8.7-20.0)		14.4 (8.7-20.1)	
>12 y	114/844	13.3 (10.4-16.1)		13.3 (10.3-16.2)	
Residential region			1.00		1.00
Northeast	21/152	13.9 (8.6-19.2)		14.0 (8.6-19.3)	
Midwest	69/502	13.8 (10.7-16.9)		13.7 (10.6-16.8)	
South	65/471	13.8 (10.6-17.1)		13.8 (10.6-17.0)	
West	38/237	16.0 (10.9-21.1)		16.1 (11.0-21.2)	
Hypertension			<0.001		0.001
Yes	72/354	19.9 (15.6-24.3)		20.0 (14.8-25.2)	
No	121/1,011	11.8 (9.4-14.2)		11.8 (9.3-14.3)	
Obesity			<0.001		<0.001
Yes	113/607	18.4 (15.1-21.8)		18.3 (14.8-21.8)	
No	80/753	10.5 (7.7-13.2)		10.5 (7.7-13.3)	
Diabetes			0.09		0.14
Yes	20/90	21.3 (12.8-29.8)		20.5 (11.9-29.1)	
No	173/1,275	13.4 (10.7-16.0)		13.4 (10.6-16.2)	
Tobacco use (ever)			0.93		0.98
Yes	57/395	14.0 (10.0-17.9)		13.8 (9.7-17.9)	
No	134/962	13.8 (11.4-16.2)		13.9 (11.3-16.5)	
Alcohol use (ever) and consume >5 drinks/occasion			0.46		0.55
Yes	11/96	11.5 (5.1-17.9)		11.9 (5.1-18.7)	
No	179/1,255	14.0 (11.4-16.6)		14.0 (11.3-16.7)	
Amphetamine use (ever)			0.56		0.62
Yes	6/50	11.4 (2.6-20.1)		11.6 (2.3-20.9)	
No	185/1,307	13.9 (11.4-16.5)		13.9 (11.3-16.6)	
Cocaine use (ever)			0.47		0.50
Yes	9/51	17.3 (8.4-26.3)		17.2 (7.6-26.8)	
No	182/1,306	13.7 (11.0-16.3)		13.7 (11.0-16.5)	

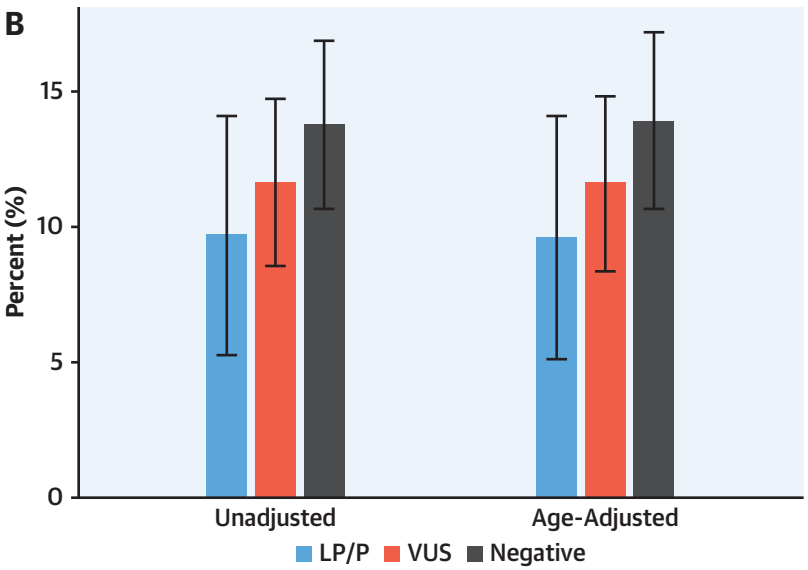
[a]Percentages and Wald 95% CIs were obtained from generalized estimating-equation type generalized logistic mixed models accounting for site heterogeneity and intrafamily correlation for different subgroups except residential region, which is modeled using generalized estimating-equation model caused by its high correlation with site. Percentages derived from this model fit apply to first-degree relatives of patients seen at a typical U.S. advanced heart failure program, defined as a program at the mean or mode of the random effects distribution describing the population of such programs. Age-adjusted percentage is estimated using the marginal standardization method, in which the predicted probability is a weighted average over the distribution of the enrollment age group. Wald *P* values for differences in these percentages were obtained using the delta method with a standard normal distribution. Overall *P* value for variables with more than 2 categories is the minimum of the Bonferroni-corrected *P* values for the risk differences with the reference category. [b]Non-Hispanic other group includes 1 Asian, 5 Native American or Alaskan Native, and 10 participants with more than 1 race.

Abbreviations as in Table 2.

FIGURE 3 First-Degree Relatives With DCM or Partial DCM by DCM-Related Rare Variants



Probands' Most Deleterious DCM-Related Rare Variants	n/N	Unadjusted % (95% CI)	Age-Adjusted % (95% CI)
LP/P	11/287	3.9 (1.2-6.6)	4.0 (1.1-6.9)
VUS	15/556	2.5 (1.2-3.8)	2.4 (1.1-3.8)
Negative	3/517	0.6 (0-1.2)	0.5 (0-1.2)



Probands' Most Deleterious DCM-Related Rare Variants	n/N	Unadjusted % (95% CI)	Age-Adjusted % (95% CI)
LP/P	27/287	9.4 (5.1-13.7)	9.3 (5.0-13.7)
VUS	65/556	11.5 (8.6-14.4)	11.5 (8.4-14.5)
Negative	69/517	13.3 (10.3-16.3)	13.4 (10.1-16.6)

Continued on the next page

STUDY LIMITATIONS. This analysis is based on data from the largest and most diverse DCM screening study with multicenter involvement. At the time of publication of this report, genetic data were available only from probands and the FDR clinical data were from a cross-sectional study design[2,9] that offered only a "1 point in time" opportunity to observe relevant FDR cardiovascular phenotypes. Also, the partial phenotypes of LVE or LVSD, previously predicted by others as discussed in the previous text to portend the development of DCM,[15-20] were not shown to be associated with genetic information, which also suggests that longitudinal follow-up could be exceptionally valuable in this diverse cohort. Nevertheless, this analysis is highly clinically relevant, as it mirrors the experience of most clinicians when they encounter a patient with a new DCM diagnosis, with or without genetic analysis, and that patient seeks counseling on risks of DCM to their FDRs who are not known or suspected to have DCM. Second, patients with DCM in this study were recruited from advanced heart failure programs. It is known that such patients tend to be sicker than those in primary and secondary care settings. However, it is unknown if the FDRs of these patients differ from those seen in other care settings regarding their DCM status; caution should be made when generalizing the results to patients in primary and secondary care settings. Third, this cross-sectional study can only demonstrate an association rather than a causal relationship between screen-based DCM and DCM partial phenotypes and cardiovascular risk factors. Follow-up of these FDRs will be needed to indicate causality. Fourth, only about one-third of FDRs were enrolled in the DCM Precision Medicine Study.[2] FDRs enrolled into the study may have been more health conscientious and may have had higher educational attainment. If so, the true prevalence of DCM could have been underestimated. Also, some echocardiograms were performed outside of the research setting and were not reviewed by the study cardiologists, which could result in underestimation of the prevalence. On the other hand, FDRs of probands who were sicker may have been more likely to participate in the study. If true, the screen-based percentages of DCM or partial DCMs= could have been overestimated.

CONCLUSIONS

Notwithstanding these limitations, this study has provided additional information that can be used in risk communications with probands and their at-risk family members while implementing published guidelines regarding clinical screening of FDRs of probands with DCM. Combined with concurrent genetic testing and counseling, this study supports the recommendation for clinical screening of all at-risk FDRs of patients with DCM.

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FIGURE 3 Continued

(A) Percentage of first-degree relatives (FDRs) with DCM by probands' DCM-related rare variants. **Blue, red, and gray bars** depict percentages of FDRs with DCM for the 3 DCM-related rare variant groups. Age-adjusted percentages were higher for FDRs when their probands carried likely pathogenic/pathogenic (LP/P) or variants of uncertain significance (VUS) only compared with those who did not carry any ($P = 0.045$ and 0.01, respectively). **(B)** Percentage of FDRs with LVSD or LVE by probands' DCM-related rare variants. **Blue, red, and gray bars** depict percentages of FDRs with LVE or LVSD for the 3 DCM-related rare variant groups. Age-adjusted percentages of those with LVSD or LVE for FDRs when their probands carried LP/P and VUS variants only were not statistically different from those whose probands did not carry any ($P = 0.47$ and 0.79, respectively). **Error bars** denote the 95% CI. Abbreviations as in Figure 2.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Screening of at-risk FDRs of patients with DCM can identify individuals with left ventricular enlargement and systolic dysfunction and prevent later morbidity and mortality.

TRANSLATIONAL OUTLOOK: Longitudinal studies are needed to examine the effectiveness of cardiovascular screening with genetic information among at-risk FDRs.

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APPENDIX For a supplemental table, please see the online version of this paper.