Title: Evaluation of Women with Peripartum or Dilated Cardiomyopathy and Their First-Degree Relatives: The DCM Precision Medicine Study

Authors: Evan P. Kransdorf, MD PhD;[1], Rashmi Jain, MD[1]; Jonathan O. Mead, BS,[2,3] Garrie Haas, MD,[3,4] Mark Hofmeyer, MD,[5] Gregory A. Ewald, MD,[6] Jamie Diamond, MD,[7] Anjali Owens, MD,[8] Brian Lowes, MD PhD,[9] Douglas Stoller MD PhD,[9] W. H. Wilson Tang, MD,[10] Mark Drazner, MD,[11] Cindy M. Martin, MD,[12] Palak Shah, MD MS,[13] Jose Tallaj, MD,[14] Stuart Katz, MD,[15] Javier Jimenez, MD PhD,[16] Supriya Shore, MBBS, MS,[17] Frank Smart, MD,[18] Jessica Wang, MD PhD,[19] Stephen S. Gottlieb, MD[20] Daniel P. Judge, MD,[21] Gordon S. Huggins MD,[22] Jason Cowan, PhD,[2,3] Patricia Parker, MS,[2,3] Jinwen Cao, MS,[2,3] Natalie S. Hurst, MTDA,[2,3] Elizabeth Jordan, MMSc,[2,3] Hanyu Ni, PhD MPH,[2,3] Daniel D. Kinnamon, PhD,[2,3] Ray E. Hershberger, MD.[2,3,4]

Author Affiliations: 1) Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA; 2) Division of Human Genetics, Department of Internal Medicine, The Ohio State University, Columbus, OH; 3) The Davis Heart and Lung Research Institute, The Ohio State University, Columbus, OH; 4) Division of Cardiovascular Medicine, Department of Internal Medicine, The Ohio State University, Columbus, OH; 5) Medstar Research Institute, Washington Hospital Center, Washington, DC; 6) Washington University, St. Louis, MO; 7) Emory University, Atlanta, GA; 8) Center for Inherited Cardiovascular Disease, Division of Cardiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; 9) University of Nebraska Medical Center, Omaha, NE; 10) Department of Cardiovascular Medicine, Heart, Vascular and Thoracic Institute, Cleveland Clinic, Cleveland, OH; 11) University of Texas Southwestern Medical Center, Dallas, TX; 12) Houston Methodist Hospital, Houston, TX; 13) Inova Heart and Vascular Institute, Falls Church, VA; 14) University of Alabama, Birmingham; 15) New York

University Langone Medical Center, New York, NY; 16) Miami Cardiac & Vascular Institute, Baptist Health South, Miami, FL; 17) University of Michigan Medical Center, Ann Arbor, MI; 18) Louisiana State University Health Sciences Center, New Orleans, LA; 19) University of California Los Angeles Medical Center, Los Angeles, CA; 20) University of Maryland School of Medicine, Baltimore, MD; 21) Medical University of South Carolina, Charleston, SC; 22) Cardiology Division, Tufts Medical Center and Tufts University School of Medicine, Boston, MA.

Short title: Peripartum and Dilated Cardiomyopathy

Corresponding Author: Ray E. Hershberger, MD, The Ohio State University Wexner Medical Center, Biomedical Research Tower Room 304, 460 West 12th Avenue, Columbus, OH 43210 USA. Email: Ray.Hershberger@osumc.edu

Total word count: 7300; Word count of main text: 3199.

Abstract

Background: Peripartum cardiomyopathy (PPCM) presents substantial risk of maternal mortality, but underlying cause remains unsettled.

Methods: We compared the prevalence of dilated cardiomyopathy (DCM)-relevant genetic variants in 452 female patients (probands) of African and European ancestry (AA, EA) with PPCM or DCM who had been pregnant at least once. Pathogenic and likely pathogenic (P/LP) variants were identified in DCM-associated genes. Risk of DCM or partial DCM, defined as left ventricular enlargement or a left ventricular ejection fraction of <50%, were compared in 665 FDRs of PPCM and DCM probands.

Results: The **e**stimated prevalences of P/LP findings among 67 probands with PPCM compared to 385 probands with DCM were comparable within ancestry (for AA, 7.8% [95% CI: 0.0%-15.7%] vs. 7.8% [95% CI: 1.1%-14.4%]; for EA, 29.5% [12.5%-46.5%] vs. 29.8% [15.5%-44.2%]). The risk of DCM/partial DCM was not lower for FDRs of PPCM probands relative to FDRs of DCM probands (HR, 0.77; 95% CI, 0.47 – 1.28). For an FDR of a non-Hispanic EA proband with PPCM, the lowest estimated DCM/partial DCM risk by age 80 was 26.8% (95% CI, 15.0%-45.0%) compared to 33.2% (95% CI, 21.2%-49.5%) for an FDR of a proband with DCM. Further validating PPCM genetic risk by using a set of genes common between studies, the estimated prevalence of P/LP variants among EA PPCM probands (26.6%; 95% CI, 12.6%-40.6%) was higher than the general population estimate from a UK Biobank study (0.6%), Also, the estimated DCM prevalence among the lowest-risk FDRs of non-Hispanic EA probands with PPCM (7.0% [95% CI, 0%-14.1%] females, 9.0% [95% CI, 1.6%-16.3%] males) was higher than general population estimates from another UK Biobank study (0.30% females, 0.63% males).

Conclusions: Comparing women with PPCM to those with DCM, a similar prevalence of DCM-relevant genetic variants and similar risk of DCM or partial DCM among their first-degree relatives were observed. These findings, along with comparisons to the general population showing higher prevalence of DCM-relevant genetic variants in women with PPCM and higher DCM prevalence in their FDRs, strengthen evidence for the genetic basis of PPCM and underscore the need for clinical genetic evaluations for PPCM patients.

Clinical Trial: clinicaltrials.gov, NCT03037632

Keywords: Peripartum cardiomyopathy, pregnancy-associated cardiomyopathy, dilated cardiomyopathy, genetics.

Clinical Perspective

What is new?

- This is the first study to use familial risk, as shown by DCM and partial DCM phenotypes in first-degree relatives (FDRs) of women with PPCM, to gain insight into the genetics of PPCM.
- The prevalence of DCM-relevant rare genetic variants was similar between women probands diagnosed with PPCM and DCM within European and African ancestry groups.
- In PPCM probands of European ancestry, the prevalence of rare variants in DCM-relevant genes was higher than a general population estimate.
- In the first-degree relatives of women with PPCM and DCM, the familial risk of DCM or a partial phenotype of DCM was similar for PPCM and DCM but higher than a population-based estimate.

What are the clinical implications?

- The genetic findings of this study from PPCM probands and their first-degree relatives strengthens evidence that DCM-related genetics is a key underlying factor in the risk of PPCM.
- A genetics evaluation is indicated following established guidelines for women with PPCM as is the case for women and men with DCM.

Introduction

Peripartum cardiomyopathy (PPCM) is defined as left ventricular systolic dysfunction that presents with heart failure during pregnancy or in the postpartum period without other clinically identifiable cardiovascular causes such as coronary or valvular disease.[1,2] PPCM is a significant contributor to maternal mortality.[3] Previously identified risk factors for PPCM include Black race, pre-eclampsia, hypertension, advanced maternal age, and multi-gestational pregnancies.[1,2]

The underlying cause of PPCM remains incompletely defined with alternative hypotheses suggesting genetic and/or pregnancy-related endogenous causes.[2] A genetic contribution to PPCM has been suggested based on familial clustering of PPCM.[4-6] Also, rare variants in genes associated with dilated cardiomyopathy (DCM) have been identified in women with PPCM,[5,7-9] including evidence that equivalent fractions of women with PPCM and DCM have DCM-relevant genetic findings.[7,8] However, whether endogenous factors related to the hormonal, physiologic or immunologic[10] milieu of pregnancy form the primary basis for PPCM or whether genetics constitutes the primary basis for PPCM has not been resolved.[2]

This study postulated that if PPCM resulted principally from pregnancy-related endogenous cause unrelated to heritable genetics, then the prevalence of DCM-relevant genetic findings and familial aggregation, specifically DCM risk among first-degree relatives (FDRs), among women with PPCM would be much lower than for women with DCM but comparable to the general population. Conversely, if genetics were relevant to both PPCM and DCM, then women with PPCM or DCM would have similar prevalence of DCM-relevant genetic findings and familial aggregation of DCM, both exceeding those in the general population. This was tested by evaluating all women from the DCM Precision Medicine Study who had been pregnant

121 at least once and had PPCM or DCM along with their FDRs The findings for women with PPCM
122 were also compared with general population estimates from the UK biobank study.
123
124 **Methods**
125 *Participants*
126 The DCM Precision Medicine study was a cross-sectional study of families at 25 U.S.
127 clinical sites; patients with DCM (probands) and FDRs were enrolled between June 2016 and
128 April 2021.[11,12] All probands met criteria for DCM, defined as left ventricular systolic
129 dysfunction (LVSD; left ventricular ejection fraction <50%) and left ventricular enlargement
130 (LVE) with non-genetic causes excluded.[11,12] Cardiac magnetic resonance imaging data when
131 available validated DCM diagnoses.[13] The Institutional Review Boards (IRB) at the Ohio State
132 University and all clinical sites approved the initial study, followed by single IRB oversight at
133 the University of Pennsylvania. All participants gave written informed consent.
134 Probands assigned as female at birth and with a history of pregnancy were included in
135 this analysis (Figure 1). PPCM cases were identified by clinical data review if a female proband
136 reported any cardiovascular problems during pregnancy and with a diagnosis of DCM meeting
137 the above definition during pregnancy or within five months of the post-partum period. All other
138 women probands, including those not reporting any cardiovascular problems during pregnancy,
139 were assigned to the DCM group for comparison.
140 *Data Collection*
141 Clinical data were collected and centrally adjudicated to confirm DCM, partial DCM, or
142 neither in probands and FDRs, as previously described.[12,14] Participant demographic information,
143 health history, and cardiovascular clinical data were obtained through structured interviews and

review of medical records, including data for all women regarding pregnancy history.[11,12,14] Research exome sequencing of probands was conducted and data processed as described previously.[15,16] Rare protein-altering variants in 36 genes considered relevant for DCM, including the 19 genes classified as definitive, strong and moderate evidence by the Clinical Genome Resource (ClinGen),[17] were identified and interpreted according to American College of Medical Genetics/Association for Molecular Pathology (ACMG/AMP) and Clinical Genome Resource (ClinGen)-based criteria tailored to DCM.[15,16]

The DCM Consortium is aware of issues for the collection, analysis, presentation, and discussion of race, ethnicity, and ancestry and has adopted recommended approaches.[18] Self-reported race and ethnicity data were 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 1 race, or unknown) and Hispanic ethnicity (yes, no, or unknown) categories. Genomic ancestry proportions in probands were estimated from Illumina Global Screening Array genotypes and used to assign individuals to groups based on predominant ancestry as previously described.[16] Individuals not in the African ancestry (AA) or European ancestry (EA) group were not analyzed due to small numbers (n = 29).

Statistical Analysis

Detailed statistical methods are provided in eAppendix 1. All statistical analyses were performed in SAS/STAT version 15.2 software, version 9.4 (TS1M7) of the SAS System for 64-bit Linux (SAS Institute Inc) and R version 4.2.2 (R Foundation, Vienna, Austria). Statistical tests and confidence intervals were two-sided with $\alpha = 0.05$ unless otherwise noted.

Differences in the distributions of demographic and clinical characteristics between women in the PPCM and DCM groups within proband enrollment sites were assessed using a generalized Cochran-Mantel-Haenszel test[19,20] (categorical) and the Boos-Brownie test[21] of the relative effect (continuous), both of which treat sites as random.

To estimate ancestry-specific prevalences of PPCM for a proband at a typical US advanced heart failure program, a generalized linear mixed model for a logit-linked binary outcome (PPCM or DCM) with covariates for genomic ancestry, ethnicity, and enrollment age quartile was fit to the proband data. The model included a random intercept to adjust for enrollment site heterogeneity. Marginally standardized prevalence estimates at a typical US advanced heart failure program were calculated for probands of AA and EA as described in eAppendix 1.

To investigate the potential association between PPCM status and DCM-relevant rare variant findings, trinomial outcomes were defined for each proband based on the number of variants classified as Pathogenic, Likely Pathogenic or Variant of Uncertain Significance (P/LP/VUS; 0, 1, or >1) and the most deleterious variant identified (none, VUS, or P/LP). These outcomes were modeled using a previously published hierarchical logit mixed model[16] with PPCM status, ancestry group (AA or EA), ethnicity (Hispanic or non-Hispanic), and quartile of age at DCM diagnosis as fixed effects and proband enrollment site random effects to account for potential site heterogeneity. The Morel-Bokossa-Neerchal bias-corrected empirical covariance estimator with sites as independent units was used to counter the well-known downward bias in model-based covariance estimates.[22,23] In addition to odds ratios comparing groups, this model fit was used to obtain marginally standardized estimates of outcome probabilities at a typical US advanced heart failure program, as described in eAppendix 1. In addition, a logistic regression

model with PPCM status, ancestry group (AA or EA), ethnicity (Hispanic or non-Hispanic), and quartile of age at DCM diagnosis fixed effects was used to estimate the prevalence of P/LP findings in the population of PPCM probands for comparison with a general population prevalence estimate from a prior UK Biobank study,[24] as described in eAppendix 1.

Variants were grouped by the PPCM classification of the study proband(s) in whom they were identified (PPCM, DCM, or both). Variant characteristics were compared using the exact Pearson X^2 test for nominal variables and the Kruskal-Wallis test for continuous variables. For post hoc pairwise comparisons between ancestries, Holm-Bonferroni corrected exact Monte-Carlo p-values for the X^2 test involving only those 2 groups or Dwass-Steel-Critchlow-Fligner multiplicity-adjusted p-values based on pairwise Wilcoxon rank sum tests were used.[25,26] The exact Monte Carlo p-value estimate based on 100,000 replicates was used for the Pearson X^2 test.

Data on the DCM or partial DCM status of each enrolled FDR at enrollment was used to model age-specific cumulative risks using a previously published approach.[12] In this approach, the unobserved age at disease onset in FDRs was assumed to have a marginal distribution with a Weibull baseline survivor function influenced by covariates and site random effects through a proportional hazards model. Covariates included proband PPCM status, genomic ancestry group, ethnicity, and age at diagnosis quartile and first-degree relative biological sex. This model was fit as a generalized estimating equation-type generalized linear mixed model[23,27] with a binary outcome (presence or absence of DCM or DCM/partial DCM), complementary log-log link, and working independence correlation structure using residual subject specific pseudolikelihood; intra-familial correlation was accounted for by using the Morel-Bokossa-Neerchal bias-corrected empirical covariance estimator with sites as independent units.[22] In addition to conditional

hazard ratios comparing groups at a particular site, this model fit was used to obtain estimates of age-specific cumulative risk among the lowest-risk FDRs of non-Hispanic EA probands with PPCM or DCM at a typical US advanced heart failure program and to estimate DCM prevalence among such FDRs of PPCM patients seen at these programs for comparison to general population DCM prevalence estimates from a prior UK Biobank study,[28] as detailed in eAppendix 1.

Results

Of 1203 probands, 452 female probands with ≥1 pregnancy were evaluated (Figure 1), including 67 with PPCM and 385 with DCM. The principal differences observed between women with PPCM and DCM were an earlier age of diagnosis and earlier age of study enrollment. (Table 1). There was a higher percentage of Black (self-identified) probands in the PPCM group, but these differences were not statistically significant.

Of 452 female probands, 665 FDRs were available for analysis (Table 2). The demographics of both groups were similar regardless of their proband's assignment as PPCM or DCM.

Ancestry-specific PPCM prevalence estimates in probands

The prevalence of PPCM was estimated separately for AA and EA probands using the model in eTable 1. Among AA probands the estimated prevalence of PPCM was 16.8% (95% CI, 11.1% - 22.6%). For a similar population of EA probands, the estimated prevalence was 14.4% (95% CI, 7.6% - 21.2%). The mean difference in PPCM prevalence between ancestries was 2.4% (95% CI, -6.8% - 11.6%), with no statistically significant difference.

Genetic findings in probands with PPCM versus DCM

A detailed tabulation of P/LP/VUS variants by gene and PPCM status of the proband(s) in whom they were found is provided (eTable 2). The model-based estimates of the prevalence of harboring a variant classified as P/LP/VUS among AA and EA probands with PPCM were 55.4% (95% CI, 33.1%-77.7%) and 66.0% (95% CI, 38.6%-93.3%), respectively (Table 3). These prevalences were similar among probands with DCM within each ancestry (Table 3), reflecting similar odds of P/LP/VUS findings in probands with PPCM or DCM (OR, 0.79; 95% CI, 0.25-2.49; Table 4).

The prevalence of harboring a variant classified as P/LP among AA and EA probands with PPCM were 7.8% (95% CI, 0.0%-15.7%) and 29.5% (95% CI, 12.5%-46.5%), respectively (Table 3). The difference in prevalence by ancestry reflected substantially lower odds of having at least 1 P/LP for AA compared to EA probands with at least 1 P/LP/VUS variant (OR, 0.20; 95% CI, 0.09-0.44; Table 4). The prevalence of harboring a P/LP variant was similar in probands with PPCM and DCM within each ancestry group, reflecting similar odds of harboring P/LP/VUS variant noted above as well as similar odds of a P/LP variant among probands with at least 1 P/LP/VUS variant (OR, 1.12; 95% CI, 0.39-3.24; Table 4). The prevalence of P/LP variants among the population of EA probands with PPCM was 26.6% (95% CI, 12.6% - 40.6%) compared with 0.6% in the general population as represented in a UK Biobank study[24] (Supplemental Methods, eAppendix 1).

P/LP/VUS variants were classified depending on the PPCM classification of the proband(s) in which they were found and their characteristics compared (eTable 3). Variants found only in the PPCM group were comparable in terms of pathogenicity classification, gene evidence category, and predicted impact to those found only in the DCM group. Those found only in the PPCM group were similar to those found only in the DCM group in terms of

interpretation criteria met, although the former had higher maximum alternate allele frequency in gnomAD non-founder populations (eTable 4).

Familial aggregation in PPCM versus DCM

FDRs of AA probands had higher hazard of both DCM (Table e5) and DCM/partial DCM (Table 5) than FDRs of EA probands after adjusting for FDR sex, proband enrollment site, proband ethnicity, proband PPCM status, and proband diagnosis age quartile. The hazard of DCM/partial DCM was also higher for FDRs of probands diagnosed at younger ages (Table 5). Nonetheless, there was no evidence supporting reduced familial aggregation in FDRs of PPCM probands relative to those of female DCM probands for either DCM (hazard ratio, 0.58; 95% CI, 0.23 – 1.47; eTable 5) or DCM/partial DCM (hazard ratio, 0.77; 95% CI, 0.47 – 1.28; Table 5, Figure 2b). For an FDR of a non-Hispanic EA proband with PPCM, the lowest estimated DCM/partial DCM risk by age 80 was 26.8% (95% CI, 15.0%-45.0%) compared to 33.2% (95% CI, 21.2%-49.5%) for an FDR of a proband with DCM (Figure 2). For DCM risk by age 80, the corresponding estimates were 12.2% (95% CI, 4.5%-30.4%) and 20.0% (95% CI, 10.8%-35.3%). For a non-Hispanic EA proband with PPCM, DCM prevalence among FDRs in the lowest risk category aged 40-69 years estimated from this model (7.0% [95% CI, 0%-14.1%] females, 9.0% [95% CI, 1.6%-16.3%] males) was higher than general population estimates (0.30% females, 0.63% males) from a prior UK Biobank study.[28]

Discussion

This study revealed that the DCM-relevant genetic findings of women with PPCM were similar to women with DCM and higher than the general population. Moreover, the family-based design of the DCM Precision Medicine study offered a unique opportunity to evaluate familial

aggregation--that is, to assess risk of DCM in FDRs--which is a powerful indicator of shared genetic risk. If PPCM would be due primarily to pregnancy-related endogenous causation unrelated to DCM genetics, then DCM risk in the FDRs of PPCM probands should be more similar to the general population than to FDRs of DCM probands. That result was not observed, with FDRs of PPCM probands having an estimated DCM prevalence higher than the general population and with hazard not significantly lower than FDRs of DCM probands (adjusted hazard ratio 0.58; 95% CI, 0.23 – 1.47). Taken together, these two complementary lines of evidence suggest a key role for DCM genetics in PPCM.

These findings are highly relevant for the clinical care of women because they suggest that with a PPCM diagnosis a genetic evaluation is indicated,[29] which includes a careful family history for cardiovascular disease and genetic testing with pre- and post-test counseling. The knowledge derived from such a genetic evaluation will directly contribute to the care of the patient's cardiomyopathy and may also inform her considerations for possible future pregnancies. Genetic information also can contribute to family-based care, including risk assessments for heritable cardiomyopathies in FDRs,[29] including any children of a PPCM patient.

The findings of this study are also highly relevant for public health, as PPCM is a leading cause of maternal mortality,[3] and maternal mortality driven in large part by PPCM is higher in Black women for a variety of reasons beyond genetics, including social determinants of health.[3,30-32] The evidence provided here that DCM genetics are also key to assessing PPCM risk is relevant for all women with PPCM, but particularly so for women of AA due to shortcomings in access, genetic testing, and genetic databases for non-European individuals.[33,34] Complicating genetic assessments of PPCM and DCM for individuals of AA are differences in the genetic

304 architecture of DCM in AA versus EA,[16] as the fraction and number of P/LP variants,
305 particularly of *TTN* truncating variants, were lower in probands of AA compared to EA.[16] While
306 the data from this study did not show increased risk of PPCM in women of AA compared to
307 women of EA, prior data suggest that DCM risk more generally may be increased in individuals
308 of AA relative to individuals of EA. Our findings of increased age-specific cumulative risks of
309 DCM (HR 2.18, 95% CI 1.39 - 3.43, p = 0.001) and DCM/partial DCM (HR of 1.45; 95% CI
310 1.04 – 2.01; p = 0.03) among FDRs of AA women probands shown in this study support this
311 possibility. An earlier case-control study also observed an increased risk in both men and women
312 patients of AA with DCM.[35] Our prior family-based observations also support a possible
313 increased risk of DCM in AA, where the estimated prevalence of familial DCM was higher in
314 Black probands than in White probands (difference 11.3%, 95% CI, 1.9% - 20.8%) and the
315 model-based estimates of age-specific cumulative risk were higher in FDRs of Black probands
316 compared to those of White probands.[12]

317 This study was focused exclusively on assessing the underlying cause of PPCM/DCM
318 and not on factors that modify the penetrance or expressivity of PPCM. Importantly, only women
319 probands who had been pregnant at least once were included in the current analysis so that all
320 probands would have been exposed to any risk arising from pregnancy. Our observation of
321 similar frequencies of P/LP variants in patients with either PPCM or DCM has been previously
322 reported,[7,8] which also supports the conclusion that genetics likely underlies PPCM. The
323 availability of both PPCM and DCM groups enrolled with the same inclusion/exclusion criteria
324 is a strength of our study, whereas previous studies of PPCM have been less able to directly
325 compare PPCM to DCM.

This study is limited in that PPCM patients with left ventricular dysfunction but without dilation would have been excluded, as left ventricular dysfunction and dilation were inclusion criteria for all probands, and a smaller left ventricular diameter has been associated with increased likelihood of recovery of function.[36] Also, since probands were recruited from advanced heart failure clinics, our results may not be generalizable to all PPCM patients. Nevertheless, the PPCM patients reported here represent a cohort with advanced disease and undoubtedly an outsized contribution to maternal morbidity and mortality, providing relevant findings for the field.

Conclusion

Genetic findings among women with PPCM were similar to women with DCM, as were the age-specific cumulative risks of DCM or partial DCM in their FDRs. Also, both the prevalence of P/LP findings among women with PPCM and the prevalence of DCM in their FDRs were higher than the general population. These findings provide complementary lines of evidence supporting a role for DCM-related genetic cause, suggest that non-genetic pregnancy-related conditions may have been a less relevant contributor to PPCM in this cohort, and extend previous data suggesting a predominant role for DCM genetics. The data suggest that genetic evaluations are indicated for all women with PPCM.

ACKNOWLEDGEMENTS

The investigators thank the families with DCM who have participated in this study, without whom this effort would not be possible. The DCM Precision Medicine Study was supported by computational infrastructure provided by The Ohio State University Division of Human Genetics

Data Management Platform and the Ohio Supercomputer Center. Drs Kinnamon and Hershberger had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

FUNDING

Research reported in this publication was supported by a parent award from the National Heart, Lung, And Blood Institute of the National Institutes of Health under Award Number R01HL128857 to Dr. Hershberger, which included a supplement from the National Human Genome Research Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Support was also provided to the DCM Research Project from the Graciano Family Fund.

CONFLICT OF INTEREST

The authors declare no conflicts. The authors declare no competing interests.

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Table 1. Demographic and clinical characteristics of female probands with DCM, by PPCM classification

	PPCM N = 67	DCM N = 385	P value[b]
Characteristic			
Predominant genomic ancestry,[a] No. (%)			
African	38 (56.7)	167 (43.4)	0.33
European	29 (43.3)	218 (56.6)	
Self-identified race, No. (%)			
Black	38 (56.7)	171 (44.4)	
White	29 (43.3)	213 (55.3)	0.43
More than one race	0 (0.0)	1 (0.3)	
Continental ancestry proportion, mean (SD)			
African	0.48 (0.41)	0.37 (0.40)	0.15
European	0.47 (0.40)	0.59 (0.39)	0.28
Native American	0.02 (0.07)	0.02 (0.06)	0.43
East Asian	0.01 (0.01)	0.01 (0.03)	0.18
South Asian	0.02 (0.03)	0.02 (0.02)	0.001
Self-identified Hispanic ethnicity, No. (%)	6 (9.0)	20 (5.2)	0.19
Age at enrollment, years, median (IQR)	41.6 (33.1 – 48.6)	56.2 (46.2 – 64.5)	<0.001
Age at diagnosis, years, median (IQR)	29.7 (24.4 – 34.5)	47.4 (39.8 – 55.6)	<0.001
BMI, median (IQR)	29.8 (26.2 – 36.3)	30.3 (26.1 – 35.7)	0.40
Comorbidities, No. (%)			
Hypertension	28 (41.8)	202 (52.5)	0.051
High cholesterol	8 (11.9)	110 (28.6)	0.005
Diabetes	15 (22.4)	92 (23.9)	0.57
Cancer	1 (1.5)	17 (4.4)	0.33
Lung disease	2 (3.0)	25 (6.5)	0.32
Asthma	11 (16.4)	75 (19.5)	0.32
Presenting symptoms, No. / No. avail. (%)			
Dyspnea on exertion	26 / 66 (39.4)	166 / 384 (43.2)	0.76
Edema	19 / 66 (28.8)	104 / 384 (27.1)	0.45
Orthopnea	17 / 66 (25.8)	105 / 384 (27.3)	0.69
Weight gain	13 / 66 (19.7)	76 / 384 (19.8)	0.87
Fatigue	25 / 66 (37.9)	164 / 384 (42.7)	0.26
Palpitations	20 / 66 (30.3)	99 / 384 (25.8)	0.35

Syncope	4 / 66 (6.1)	37 / 384 (9.6)	0.25
Arrhythmia	10 / 66 (15.2)	62 / 384 (16.2)	0.85
Asymptomatic	0 / 66 (0.0)	19 / 384 (5.0)	0.02
Blood pressure measures, median (IQR) [No. avail.][c]			
Systolic (mmHg)	112 (100 – 120) [55]	114 (103 – 126) [319]	0.51
Diastolic (mmHg)	72 (63 – 78) [55]	70 (63 – 77) [319]	0.80
Mean arterial (mmHg)	85 (77 – 92) [55]	85 (77 – 93) [319]	0.88
Left ventricular ejection fraction (%), median (IQR) [No. avail.][d]	23.0 (17.5 – 32.5) [66]	22.5 (16.0 – 30.0)	0.79
Left ventricular internal diastolic dimension (mm), median (IQR) [No. avail.][d]	61.0 (57.1 – 70.0) [66]	61.0 (57.0 – 68.0)	0.52
Left ventricular internal diastolic dimension (z-score), median (IQR) [No. avail.][d,e]	4.4 (3.3 – 6.1) [66]	4.4 (3.2 – 5.9)	0.64
Interventions, No. / No avail. (%)[d]			
Left ventricular assist device	10 (14.9)	66 (17.1)	0.91
Heart transplant	8 (11.9)	40 (10.4)	0.51
Bi-ventricular pacemaker	5 / 66 (7.6)	67 / 371 (18.1)	0.13
Implantable cardioverter defibrillator	42 / 65 (64.6)	255 / 383 (66.6)	0.58

BMI = body mass index; DCM = dilated cardiomyopathy; IQR = interquartile range; PPCM = peripartum cardiomyopathy; SD = standard deviation.

[a] Genomic ancestry was determined based on global ancestry proportions inferred from array-based genotypes; an individual's predominant ancestry group was defined as the continental ancestry group (African, East Asian, European, Native American, or South Asian) accounting for the highest proportion of their genomic ancestry. Individuals with predominant continental ancestry other than African or European ancestry were not analyzed due to small numbers (see Methods).

[b] For categorical variables, two-sided p-values are from a generalized Cochran-Mantel-Haenszel test using the general association statistic, which is designed to detect within-site differences in the distribution of the row variable between PPCM and DCM that are consistent across sites. For continuous variables, two-sided p-values are from the Boos-Brownie test of the relative effect, which is designed to detect whether values in the PPCM group are systematically higher or lower than in the DCM group consistently across sites. Both tests use proband enrollment sites as the primary sampling units.

[c] Does not include measurements recorded after left ventricular assist device placement.

[d] The number available is not provided if it equates to the sample size defined in the column header.

[e] Calculated based on sex and height for all probands with heights of at least 137 cm.

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Table 2. Demographic and clinical characteristics of first-degree relatives of female probands with DCM, by proband PPCM classification

	PPCM Proband N = 103	DCM Proband N = 562
Characteristic		
Biological sex, No. (%)		
Female	68 (66.0)	354 (63.0)
Male	35 (34.0)	208 (37.0)
Relationship to proband, No. (%)		
Parent	31 (30.1)	66 (11.7)
Full sibling	17 (16.5)	149 (26.5)
Child	55 (53.4)	347 (61.7)
DCM phenotype, No. (%)		
DCM	7 (6.8)	52 (9.3)
Left ventricular enlargement only	10 (9.7)	47 (8.4)
Left ventricular systolic dysfunction only	3 (2.9)	21 (3.7)
Normal	83 (80.6)	442 (78.7)
Age at enrollment, years, median (IQR)	34.5 (17.5 – 58.5)	38.9 (27.6 – 56.1)
Left ventricular ejection fraction (%), median (IQR) [No. avail.]	60.0 (55.0 – 65.0) [101]	58.0 (55.0 – 62.5) [555]
Left ventricular internal diastolic dimension (mm), median (IQR) [No. avail.]	48.0 (44.0 – 52.0) [100]	48.0 (44.0 – 52.0) [554]
Left ventricular internal diastolic dimension (z-score), median (IQR) [No. avail.][a]	0.1 (-1.1 – 1.4) [96]	0.0 (-1.0 – 1.2) [544]

DCM = dilated cardiomyopathy; IQR = interquartile range; PPCM = Peripartum cardiomyopathy.
[a] Calculated based on sex and height for all first-degree relatives with heights of at least 152 cm (male) or 137 cm (female).

Table 3. Variant classification results in female probands, by ancestry and PPCM classification

	African N = 205				European N = 247			
	PPCM N = 38		DCM N = 167		PPCM N = 29		DCM N = 218	
	Crude	Model-based[a]	Crude	Model-based[a]	Crude	Model-based[a]	Crude	Model-based[a]
Outcome	No. (%)	% (Joint 95% CI)	No. (%)	% (Joint 95% CI)	No. (%)	% (Joint 95% CI)	No. (%)	% (Joint 95% CI)
Most deleterious variant identified								
None	15 (39.5)	44.6 (22.3 – 66.9)	77 (46.1)	38.9 (19.7 – 58.2)	11 (37.9)	34.0 (6.7 – 61.4)	77 (35.3)	29.0 (18.5 – 39.6)
VUS	19 (50.0)	47.7 (25.2 – 70.1)	78 (46.7)	53.3 (32.5 – 74.1)	10 (34.5)	36.4 (7.9 – 64.9)	80 (36.7)	41.2 (27.5 – 54.8)
P/LP	4 (10.5)	7.8 (0.0 – 15.7)	12 (7.2)	7.8 (1.1 – 14.4)	8 (27.6)	29.5 (12.5 – 46.5)	61 (28.0)	29.8 (15.5 – 44.2)
Number of P/LP/VUS variants identified								
None	15 (39.5)	44.6 (22.4 – 66.7)	77 (46.1)	38.9 (19.8 – 58.1)	11 (37.9)	34.0 (6.8 – 61.3)	77 (35.3)	29.0 (18.6 – 39.4)
1	18 (47.4)	43.2 (19.2 – 67.3)	63 (37.7)	41.4 (24.8 – 58.0)	13 (44.8)	47.8 (16.0 – 79.7)	90 (41.3)	43.3 (31.6 – 55.0)
>1	5 (13.2)	12.2 (1.4 – 23.0)	27 (16.2)	19.7 (9.2 – 30.1)	5 (17.2)	18.1 (4.3 – 32.0)	51 (23.4)	27.7 (17.2 – 38.2)

CI = confidence interval; DCM = dilated cardiomyopathy; LP = likely pathogenic; P = pathogenic; PPCM = peripartum cardiomyopathy; VUS = variant of uncertain significance.

[a] Estimates from hierarchical logit mixed models for trinomial outcomes presented in Table 4 and the Morel-Bokossa-Neerchal bias-corrected estimate of their empirical covariance matrix with sites as independent units were used to obtain marginally standardized estimates of and delta method joint 95% CIs for outcome probabilities for female probands in a particular ancestry group and PPCM classification. All CIs were produced using the standard normal distribution and the Bonferroni correction over the 3 possible outcome categories. Each patient subpopulation defined by ancestry group and PPCM status was assumed to be balanced across the two youngest age quartiles (≤44.47 years of age) with a proportion of Hispanics equal to the 2021 US census population estimate (18.9%).[37] As evidence of site heterogeneity was found in both models, these estimates can be interpreted as applicable to patients seen at a typical US advanced heart failure program, defined as a program at the mean or mode of the random effects distribution describing the population of such programs.

Table 4. Associations of PPCM classification, ancestry, ethnicity, sex, and age at diagnosis with variant classification results in probands.

	Most Deleterious Variant				Number of Variants			
	P/LP/VUS vs. None		P/LP vs. VUS Given P/LP/VUS		>=1 P/LP/VUS vs. None		>1 Variant vs. 1 Variant Given >=1 P/LP/VUS	
Predictor	**Odds Ratio (95% CI)[a,b]**	**P[a]**	**Odds Ratio (95% CI)[a,c]**	**P[a]**	**Odds Ratio (95% CI)[a,b]**	**P[a]**	**Odds Ratio (95% CI)[a,c]**	**P[a]**
PPCM classification								
PPCM	0.79 (0.25 – 2.49)	0.69	1.12 (0.39 – 3.24)	0.84	0.79 (0.25 – 2.48)	0.69	0.59 (0.19 – 1.85)	0.37
DCM	1.00	-	1.00	-	1.00	-	1.00	-
Ancestry group								
African	0.64 (0.37 – 1.12)	0.12	0.20 (0.09 – 0.44)	<0.001	0.64 (0.37 – 1.12)	0.12	0.74 (0.44 – 1.25)	0.26
European	1.00	-	1.00	-	1.00	-	1.00	-
Self-reported ethnicity								
Hispanic	1.11 (0.35 – 3.57)	0.86	0.76 (0.23 – 2.50)	0.66	1.11 (0.35 – 3.54)	0.86	1.47 (0.48 – 4.53)	0.50
Non-Hispanic	1.00	-	1.00	-	1.00	-	1.00	-
Diagnosis age quartile								
I: [9.78, 34.99]	1.00	-	1.00	-	1.00	-	1.00	-
II: [35.01, 44.47]	0.82 (0.43 – 1.58)	0.55	0.75 (0.32 – 1.73)	0.50	0.82 (0.43 – 1.56)	0.55	0.89 (0.34 – 2.36)	0.82
III: [44.48, 54.09]	0.65 (0.32 – 1.34)	0.25	0.89 (0.32 – 2.45)	0.83	0.65 (0.32 – 1.33)	0.24	0.72 (0.28 – 1.82)	0.49
IV: [54.21, 78.31]	0.50 (0.27 – 0.95)	0.03	1.00 (0.33 – 3.05)	1.00	0.50 (0.27 – 0.94)	0.03	1.05 (0.35 – 3.12)	0.93

CI = confidence interval; DCM = dilated cardiomyopathy; LP = likely pathogenic; P = pathogenic; PPCM = peripartum cardiomyopathy; VUS = variant of uncertain significance.

[a] Odds ratios and Wald 95% CIs from hierarchical logit mixed models for trinomial outcomes based on the most deleterious P/LP/VUS variant identified (none, VUS, or P/LP) and the number of P/LP/VUS variants identified (0, 1, or >1) were adjusted for all other variables shown in the table. Two-sided Wald p-values are for the null hypothesis that the odds ratio is 1. All p-values and CIs were produced using the Morel-Bokossa-Neerchal bias-corrected estimate of the empirical covariance matrix and the standard normal distribution.

[b] As evidence of site heterogeneity was found, these estimates can be interpreted as comparing DCM patients within the same US advanced heart failure program.

[c] As no evidence of site heterogeneity was found, these estimates can be interpreted as comparing DCM patients within the same US advanced heart failure program or between

any two such programs.

Table 5. Model fit for age-specific cumulative risk of DCM or partial DCM in a first-degree relative of a female proband with PPCM or DCM

Parameter[a]	Estimate	Standard Error	Hazard Ratio (95% CI)	P
Fixed Effects				
Weibull baseline survivor function parameters[b]				
a	-4.0830	0.7915	-	-
b	0.7436	0.2286	-	-
Proband PPCM classification				
PPCM	-0.2575	0.2570	0.77 (0.47 - 1.28)	0.32
DCM	0	-	1.00	-
First-degree relative sex				
Female	0.06483	0.2365	1.07 (0.67 - 1.70)	0.78
Male	0	-	1.00	-
Proband ancestry group				
African Ancestry	0.3688	0.1680	1.45 (1.04 - 2.01)	0.03
European Ancestry	0	-	1.00	-
Proband self-reported ethnicity				
Hispanic	-0.2249	0.3976	0.80 (0.37 – 1.74)	0.57
Non-Hispanic	0	-	1.00	-
Proband diagnosis age				
I: [9.78, 34.99]	0	-	1.00	-
II: [35.01, 44.47]	-0.08501	0.3033	0.92 (0.51 – 1.66)	0.78
III: [44.48, 54.09]	-0.1198	0.3100	0.89 (0.48 – 1.63)	0.70
IV: [54.21, 78.31]	-0.5965	0.3070	0.55 (0.30 – 1.01)	0.052
Variance Components				
Site (σ^2_{site})	0.03904	0.05139	-	-
Residual	0.9958	0.05543	-	-

CI = confidence interval; DCM = dilated cardiomyopathy; PPCM = peripartum cardiomyopathy.

[a] Parameters of a Weibull proportional hazards model for age-specific cumulative risk were estimated using a generalized estimating equation-type generalized linear mixed model with a binary outcome (presence or absence of DCM/partial DCM), complementary log-log link, random proband enrollment site intercept, and working independence correlation structure fit using residual subject specific pseudolikelihood. Bias-corrected robust standard errors were obtained using the Morel-Bokossa-Neerchal correction with sites as independent units. Two-sided p-values and Wald 95% confidence intervals were calculated using the standard normal distribution. Hazard ratios and their 95% confidence intervals were obtained by exponentiating corresponding estimates on the model

scale.

[b] a and b are parameters of the Weibull baseline survivor function of the form $S_o(t) = \exp[-\exp(a)t^b]$. 665 first-degree relatives (103 of PPCM probands and 562 of DCM probands) contributed to this analysis.

Figure 1. Selection of DCM Precision Medicine Study participants for analysis

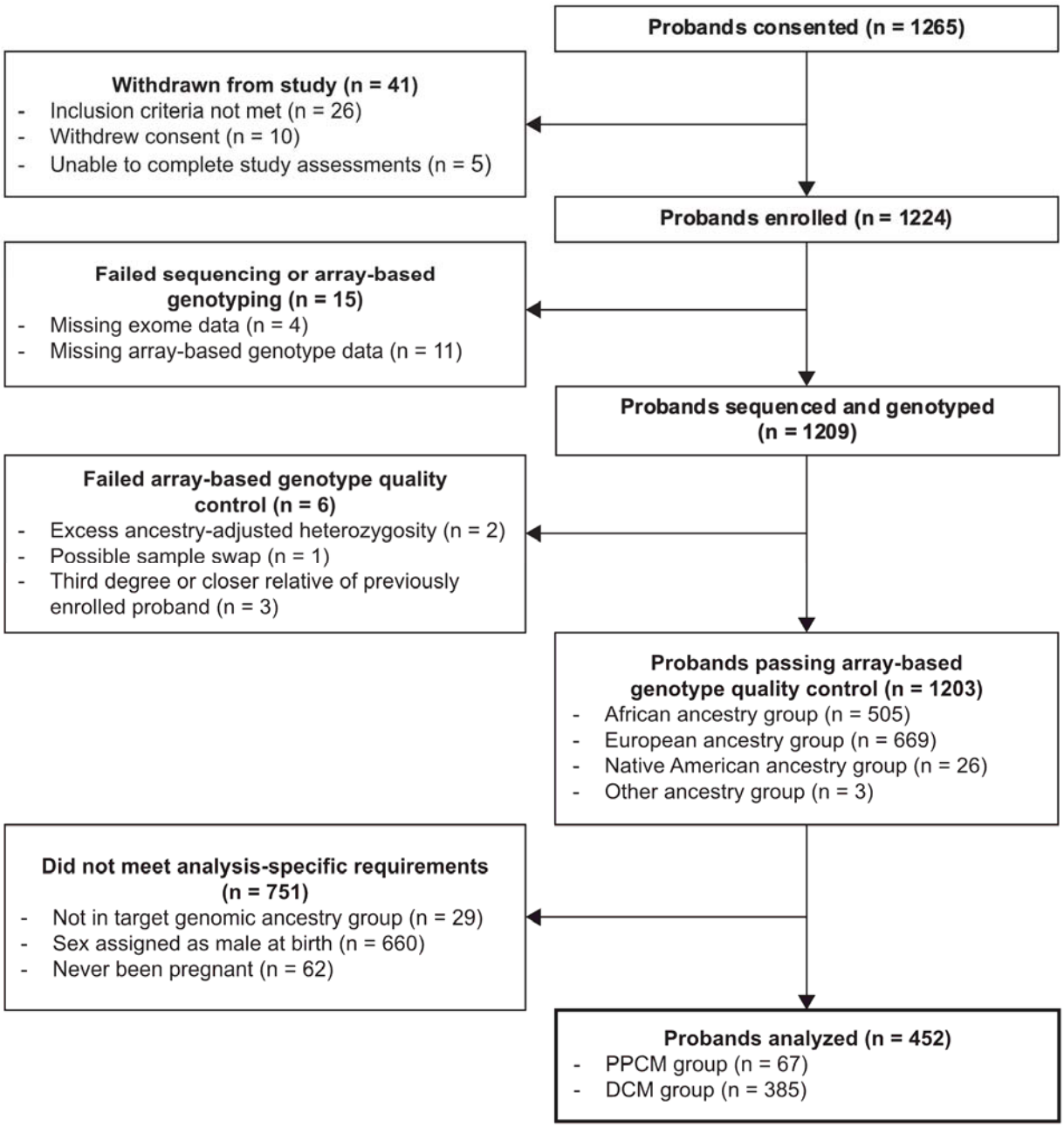

Figure 2. Model-based estimates of age-specific cumulative risk of DCM/partial DCM among the lowest-risk first-degree relatives of probands with either PPCM or DCM.

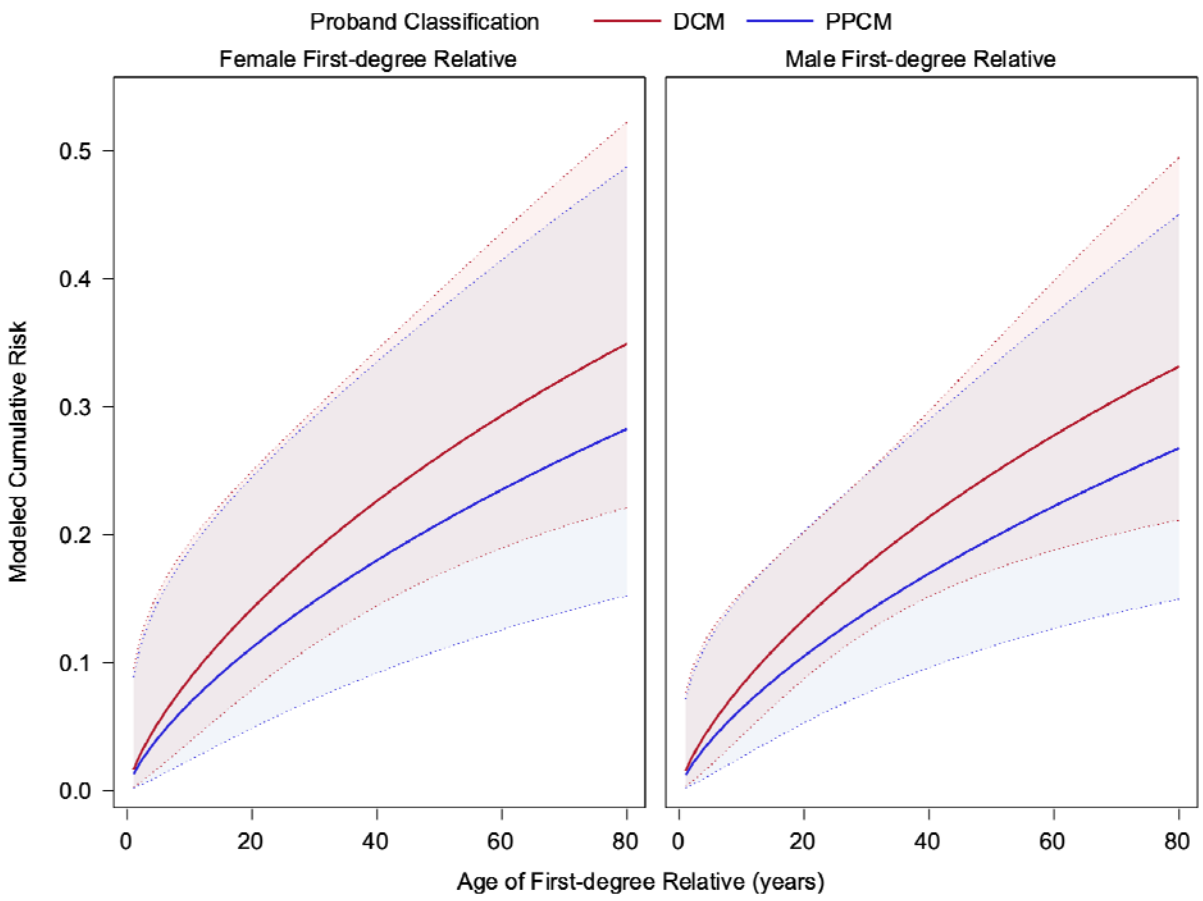

Figure legend. A Weibull proportional hazards model for age-specific cumulative risk was fit to cross-sectional data on disease status at enrollment from first-degree relatives (Table 5). Age-specific cumulative risks and 95% confidence intervals of DCM/partial DCM are presented for female and male first-degree relatives of female Non-Hispanic European probands diagnosed with DCM or PPCM between ages 35.01 and 44.47 years seen at a typical US advanced heart failure program, defined as one at the mean or mode of the random effects distribution describing the population of such programs.