

EDITORIAL COMMENT

# Genotype-Based Risk Stratification Can Outperform Phenotype-Based Practice for Inherited Cardiomyopathies



## Not All Paths Are Equal\*

Cynthia A. James, PhD, CGC, Alessio Gasperetti, MD

It is often said that truth is in the eye of the beholder. For cardiomyopathies (CMP), the diagnostic truth is usually considered found via fulfillment of a predetermined, recognizable, CMP phenotype with management based on diagnosis, symptoms, and clinical characteristics. Genetic testing has historically been implemented subsequent to clinical diagnosis with genotype used for family screening, and less often for diagnostic confirmation or management. However, in recent years, overlapping characteristics among different CMP phenotypes, patient evolution among CMP classifications with disease progression, as well as the fulfillment of different phenotypes in patients harboring variants in the same gene have been increasingly recognized.<sup>1</sup> This clinical and genetic heterogeneity is increasingly apparent among dilated cardiomyopathy (DCM) and arrhythmogenic cardiomyopathy (ACM) phenotypes, and is of particular importance given the necessity of risk stratification for sudden cardiac death. Nonetheless, most risk stratification strategies are phenotype-based with the relative weight of genotype and phenotype in risk stratification and management of patients largely unresolved.

It is from this perspective that we appreciate the paper by Paldino et al<sup>2</sup> in this issue of the *Journal of the American College of Cardiology*. Drawing from a cohort of 834 patients enrolled in the Familial Cardiomyopathy Registry of the University of Trieste and University of Colorado, our colleagues compared the effectiveness of genotype-based vs phenotype-based

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classification at diagnosis for prediction of clinical outcomes. To do so, the authors first assessed the association of nonhypertrophic cardiomyopathy phenotypes (DCM, arrhythmogenic right ventricular cardiomyopathy [ARVC], arrhythmogenic left ventricular cardiomyopathy [ALVC], and biventricular-arrhythmogenic cardiomyopathy [BiV]) at both presentation and follow-up with pathogenic/likely pathogenic variants in DCM and ARVC-associated genes. Only genes with a robust association with DCM and/or ARVC<sup>3,4</sup> and identified in at least 10 of the 834 patients were included in the analysis. The final variant-positive study cohort comprised 281 patients: 224 (80%) diagnosed with DCM, 28 (10%) with ARVC, and 29 (10%) with ALVC/BiV. Six gene clusters were analyzed: *TTN* (34%), sarcomere variants (*SARC*) (22%), *FLNC* (13%), *PKP2* (11%), *LMNA* (10%), and *DSP* (10%). Importantly, an additional cohort of 370 patients with variant-negative CMP was included to facilitate assessment of the overall clinical utility of genotype in differentiating outcomes. Endpoints were rigorous, with all-cause mortality or cardiac transplant as the primary outcome, and major ventricular arrhythmia (MVA) (defined as a combination of ventricular fibrillation, sustained ventricular tachycardia lasting >30 seconds, and appropriate implantable cardioverter-defibrillator intervention)

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From the Department of Medicine, Division of Cardiology, Johns Hopkins School of Medicine, Baltimore, Maryland, USA.

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and heart failure (HF) (HF death, transplant, or LVAD placement) as secondary outcomes.

The authors first characterized genotype-phenotype associations at baseline and in follow-up. Expected genotype-phenotype correlations were observed with variants in the *TTN* and *SARC* genes associated with DCM, and *PKP2* variants typically leading to ARVC. For other genes, clinical heterogeneity was substantial. At study enrollment, variants in *DSP*, *LMNA*, and *FLNC* were associated with diagnoses ranging from DCM to ALVC. Phenotypic overlap increased during follow-up, with around one-fifth of patients harboring *TTN*, *DSP*, *LMNA*, and *FLNC* variants who had a DCM phenotype at baseline, converting their phenotype to ALVC/BiV over time. Although these findings are not unexpected, a single study with well-defined inclusion criteria performing head-to-head comparisons of diagnosis and outcomes among DCM- and ACM-associated genotypes has considerable merit in confirming observations previously reported largely in single-gene or single-diagnosis studies.

Although the genotype to phenotype observations are useful, the main novelty of this study is its ambitious goal of defining the relative prognostic weight of phenotype-based vs genotype-based classification. The authors showed clinically meaningful differences in arrhythmic outcomes, mortality, and heart transplantation rates across the 6 gene groups. As expected, *LMNA* carriers were more prone to death/transplant and HF-associated outcomes, whereas *DSP*, *PKP2*, *FLNC*, and *LMNA* (combined in the paper as “arrhythmic genes”) were associated with MVAs. We found it particularly interesting that the incidence of arrhythmic events in patients with *DSP*, *LMNA*, and *FLNC* variants were similar, regardless of clinical diagnosis, given the dearth of data on these genotypes.

Next, using multivariable Cox regression, the authors established that although both genotype- and phenotype-based classifications predicted death and heart transplant, genotype provided better discrimination and was the only classification associated with the risk of arrhythmic events (MVA). This is the key finding of the study. Importantly, the authors also tested the independent prognostic value of genotype and phenotype in their expanded cohort that also included patients with variant-negative CMD. This analysis confirmed the vital nature of genotype in a more clinically applicable patient cohort.

These findings urge us to rethink the role of genotype and the timing, type, and extent of genetic testing in CMD management. Given the prognostic

value of genotype, it does not seem unreasonable to suggest more widespread testing of CMP index patients. These data also support shifting the role of genetic testing from being one among many complementary parts of a comprehensive assessment to a cornerstone for individualized risk stratification, which will require prompt genetic testing after diagnosis. Finally, the phenotypic heterogeneity described in the cohort and in particular the phenotypic evolution over time suggests the value of using broad gene panels for DCM/ACM genetic testing. Although this approach will result in an increased rate of variants of uncertain significance, it also improves detection of variants that this study shows have important prognostic implications.<sup>5</sup>

Recent consensus statements and guidelines increasingly call attention to the importance of genotype. Nonetheless, the potential for genotype-specific risk prediction for cardiomyopathies remains mostly theoretical. For example, although the impact of genotype on arrhythmia risk stratification for ARVC has recently been described,<sup>6</sup> guidelines currently suggest that patients with *DSP*-ARVC and *PKP2*-ARVC undergo a similar risk stratification process based on their fulfillment ARVC diagnostic criteria rather than on the genetic architecture behind the disease. In light of the consistent event rates observed in patients with *DSP*, *LMNA*, and *FLNC* variants regardless of phenotype, this approach seems outdated. Although more research is needed, we envision a future in which the current CMP classification system moves toward classification and management based on individual genes, variants, and disease pathways, rather than grouping patients largely by similar clinical phenotypes. The promise of this approach is highlighted in the recently published genotype-specific arrhythmia risk prediction model for p.Arg14del PLN cardiomyopathy.<sup>7</sup>

Some limitations of this study should be acknowledged. Although certainly one of the largest studies addressing this topic, the size of the overall cohort and particularly of patients with arrhythmia genes fell short for reaching unequivocally generalizable results. Relatively small sample sizes led to the arrhythmia genes being grouped for regression analysis. It is likely that the value of genotype-based classification varies importantly among these genes. Additionally, although the process for gene selection was reasonable and well-justified, several important CMD-associated genes (ie *DSG2*, *DSC2*, *TMEM43*, *PLN*, *RBM20*, *BAG3*) were excluded because of their low frequency and therefore their impact was not assessed.<sup>3,4</sup>

In summary, we want to congratulate the authors for an intriguing study. As is the case for some of the best clinical research, their findings both have immediate implications for clinical care and also suggest additional lines of research—in this case the potential for genotype-specific risk prediction. Of course, the effects of rare CMP variants in determining patient outcomes are further modified by each patient's additional genetic background, comorbidities, and lifestyle—variables that must be accounted for in risk stratification and management. Nonetheless, in this era of precision medicine, although not providing a definite answer for how to best integrate genotype and

phenotype in management of familial cardiomyopathies, these data from Paldino et al<sup>2</sup> certainly pave the way.

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**ADDRESS FOR CORRESPONDENCE:** Dr Cynthia A. James, Johns Hopkins School of Medicine, Blalock 545, 600 North Wolfe Street, Baltimore, Maryland 21287, USA. E-mail: [cjames7@jhmi.edu](mailto:cjames7@jhmi.edu). Twitter: [@gasperettimd](https://twitter.com/gasperettimd).

#### REFERENCES

1. Smith ED, Lakdawala NK, Papoutsidakis N, et al. Desmoplakin cardiomyopathy, a fibrotic and inflammatory form of cardiomyopathy distinct from typical dilated or arrhythmogenic right ventricular cardiomyopathy. *Circulation*. 2020;141:1872-1884.
2. Paldino A, Dal Ferro M, Stolfo D, et al. Prognostic prediction of genotype vs phenotype in genetic cardiomyopathies. *J Am Coll Cardiol*. 2022;80:1981-1994.
3. James CA, Jongbloed JDH, Hershberger RE, et al. International evidence-based reappraisal of genes associated with arrhythmogenic right ventricular cardiomyopathy using the Clinical Genome Resource Framework. *Circ Genom Precis Med*. 2021;14:e003273.
4. Jordan E, Peterson L, Ai T, et al. Evidence-based assessment of genes in dilated cardiomyopathy. *Circulation*. 2021;144:7-19.
5. Murray B, Tichnell C, Tandri H, et al. Influence of panel selection on yield of clinically useful variants in arrhythmogenic right ventricular cardiomyopathy families. *Circ Genom Precis Med*. 2020;13:548-550.
6. Protonotarios A, Bariani R, Cappelletto C, et al. Importance of genotype for risk stratification in arrhythmogenic right ventricular cardiomyopathy using the 2019 ARVC risk calculator. *Eur Heart J*. 2022;ehac235. <https://doi.org/10.1093/eurheartj/ehac235>.
7. Verstraelen TE, van Lint FHM, Bosman LP, et al. Prediction of ventricular arrhythmia in phospholamban p.Arg14del mutation carriers—reaching the frontiers of individual risk prediction. *Eur Heart J*. 2021;42:2842-2850.

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