Dilated cardiomyopathy: Is your patient's genotype dictating their risk?

Written by The Life Science Feed Editorial Team · Published 23 July 2026 · Edited by William Lopes

> Dilated cardiomyopathy (DCM) presents a significant clinical challenge, often progressing to heart failure and requiring advanced therapies, including transplantation. Predicting which patients will experience rapid deterioration versus those who maintain stable cardiac function remains a critical unmet need for guiding management strategies.

KEY TAKEAWAYS

- The Pivot: Specific genetic mutations, particularly in sarcomeric genes, are not merely diagnostic markers but also prognostic indicators in dilated cardiomyopathy.
- The Data: Patients with titin (TTN) truncating variants often exhibit a higher risk of adverse events, including sudden cardiac death, compared to those with other genetic causes or idiopathic DCM.
- The Action: Routine genetic testing in DCM patients can stratify risk, inform surveillance intensity, and potentially guide targeted therapeutic interventions, moving beyond a purely phenotypic approach.

Dilated cardiomyopathy, characterised by left ventricular dilation and systolic dysfunction, affects approximately 1 in 2,500 individuals. While a significant proportion of cases are idiopathic, genetic factors contribute to 30% to 50% of diagnoses. Identifying the underlying genetic cause offers more than just an etiological label; it provides crucial prognostic information that can influence clinical decision-making and patient counselling.

The spectrum of genes implicated in DCM is broad, encompassing sarcomeric, cytoskeletal, nuclear envelope, and desmosomal proteins. Historically, genetic testing primarily confirmed a diagnosis or identified familial risk. But clinicians increasingly recognise that specific genotypes correlate with distinct clinical trajectories, influencing everything from arrhythmia risk to the likelihood of transplant-free survival. This understanding shifts the paradigm from a 'one-size-fits-all' approach to a more personalised management strategy.

The Genetic Landscape of DCM

Over 100 genes associate with DCM, but a handful account for the majority of identifiable genetic causes. Mutations in sarcomeric genes, particularly TTN (titin), MYH7 (beta-myosin heavy chain), and MYBPC3 (myosin binding protein C), are among the most common. Other frequently implicated genes include LMNA (lamin A/C), PLN (phospholamban), and DSP (desmoplakin). Each gene, when mutated, can lead to distinct pathophysiological pathways and, consequently, varying clinical manifestations and prognoses.

Titin, the largest known human protein, plays a critical role in myocardial elasticity and passive force generation. Truncating variants in TTN (TTNtv) are the most common genetic cause of DCM, found in approximately 15% to

25% of sporadic cases and up to 20% of familial cases. These variants often lead to haploinsufficiency, disrupting sarcomere integrity and myocardial function. The clinical penetrance of TTNtv is variable, with some carriers remaining asymptomatic while others develop severe heart failure.

But the prognostic implications of TTNtv are not uniform. Studies have shown that patients with TTNtv often have a higher incidence of ventricular arrhythmias and a greater risk of sudden cardiac death compared to patients with idiopathic DCM. The location of the truncating variant within the titin gene also matters; variants in the A-band region, for instance, may carry a worse prognosis than those in the I-band. This granularity in genetic information allows for more refined risk stratification.

Specific Genes, Specific Risks

Mutations in LMNA, encoding lamins A and C, are particularly aggressive. These mutations are associated with a high incidence of malignant ventricular arrhythmias, progressive heart failure, and a significant risk of sudden cardiac death, often necessitating early implantation of an implantable cardioverter-defibrillator (ICD). Patients with LMNA mutations often present with conduction system disease, including atrioventricular block, at a relatively young age. The median age of onset for cardiac events in LMNA carriers is typically in the fourth decade, with rapid progression thereafter. The cumulative incidence of major adverse cardiac events (MACE) in LMNA carriers can be as high as 70% over 10 years, significantly higher than in other genetic forms of DCM.

Phospholamban (PLN) mutations, while less common than TTNtv or LMNA, are associated with a distinct and severe phenotype. These patients often develop biventricular heart failure, severe ventricular arrhythmias, and have a high rate of progression to cardiac transplantation or death. The PLN R14del mutation, prevalent in certain populations, leads to a particularly aggressive form of DCM with early onset and rapid progression. The cumulative incidence of ventricular arrhythmias in PLN R14del carriers can exceed 50% by age 40, highlighting the need for aggressive surveillance and early intervention.

Desmoplakin (DSP) mutations, traditionally associated with arrhythmogenic right ventricular cardiomyopathy (ARVC), are increasingly recognised as a cause of biventricular DCM with a high arrhythmic burden. Patients with DSP-related DCM often present with both left ventricular dysfunction and significant ventricular arrhythmias, sometimes mimicking ARVC. The risk of sudden cardiac death in these patients is substantial, underscoring the importance of genetic diagnosis for appropriate risk stratification and management.

The Role of Genetic Testing in Prognosis

Genetic testing has evolved from a research tool to a clinical necessity in DCM. Identifying a pathogenic variant allows for cascade screening of family members, enabling early detection and intervention in at-risk relatives. But its prognostic value extends beyond family screening. Knowing the specific genetic cause can guide therapeutic decisions, such as the timing of ICD implantation, the intensity of heart failure medical therapy, and the consideration of advanced therapies like mechanical circulatory support or transplantation.

For instance, in patients with LMNA mutations, current guidelines recommend consideration of ICD implantation even in the absence of severe left ventricular dysfunction, given the high arrhythmic risk. This contrasts with idiopathic DCM, where ICD implantation is typically reserved for patients with more advanced heart failure (ejection fraction d35%). The Oxford Handbook of Cardiology provides a concise overview of these nuanced guidelines.

The clinical utility of genetic testing is not without its caveats. Variants of uncertain significance (VUS) remain a challenge, requiring careful interpretation and sometimes further functional studies or segregation analysis within families. The penetrance of many DCM-associated genes is incomplete, meaning not all carriers will develop the disease, complicating risk assessment. Still, the increasing understanding of genotype-phenotype correlations is steadily reducing the proportion of VUS and improving the predictive power of genetic results.

Beyond Single Genes: Modifiers and Polygenic Risk

While single gene mutations explain a significant portion of genetic DCM, the clinical phenotype can be modified by other genetic factors and environmental influences. Polygenic risk scores, which aggregate the effects of multiple common genetic variants, are emerging as a tool to refine risk prediction, particularly in cases where a monogenic cause is not identified. These scores may help explain the variable penetrance and expressivity observed even within families carrying the same pathogenic mutation.

Environmental factors, such as viral infections, alcohol consumption, and certain cardiotoxic medications, can also interact with genetic predispositions to trigger or accelerate disease progression. A patient with a mild genetic predisposition might remain asymptomatic for decades, but an acute viral myocarditis could unmask or exacerbate their underlying genetic susceptibility, leading to overt DCM. Understanding these gene-environment interactions is crucial for comprehensive patient management.

The clinical implications of these genetic insights are profound. They move DCM management beyond a reactive approach to one that is proactive and preventive. Early identification of high-risk genotypes allows for closer surveillance, earlier initiation of guideline-directed medical therapy, and timely consideration of device therapies. This precision medicine approach aims to mitigate disease progression and improve long-term outcomes for patients with DCM.

Where the Data Falls Short

Despite the growing body of evidence, large-scale, prospective studies directly comparing outcomes based on comprehensive genetic profiles are still limited. Much of the current understanding comes from retrospective cohorts or smaller, single-centre studies. The heterogeneity of DCM phenotypes, even within the same genetic subtype, makes it challenging to establish definitive prognostic algorithms that apply universally.

The cost and accessibility of comprehensive genetic testing also remain barriers in many healthcare systems. While next-generation sequencing has reduced costs, the interpretation of results requires specialised expertise, which is not universally available. Furthermore, the psychological impact of a genetic diagnosis on patients and their families, including concerns about insurability and discrimination, requires careful consideration and genetic counselling.

The field also lacks randomised controlled trials specifically designed to test genotype-guided therapeutic interventions. Most treatment recommendations are extrapolated from general heart failure guidelines or based on observational data. Future research needs to focus on designing trials that specifically address whether genotype-informed management strategies lead to superior outcomes compared to standard care.

> **CLINICAL IMPLICATIONS**
> The era of treating dilated cardiomyopathy as a monolithic entity is drawing to a close. Genetic testing is no longer a niche diagnostic tool; it is becoming an indispensable component of comprehensive patient

evaluation, offering critical prognostic insights that should inform clinical decisions.

Clinicians should consider routine genetic screening for all DCM patients, not just those with a clear family history. Identifying specific mutations, particularly in genes like LMNA or PLN, can trigger earlier and more aggressive interventions, such as ICD implantation, potentially preventing sudden cardiac death. This moves beyond the traditional reliance on ejection fraction alone for risk stratification.

The challenge lies in integrating this complex genetic information into everyday practice. Interpretation of genetic reports requires expertise, and the management implications are still evolving. But the data clearly indicate that ignoring a patient's genotype means missing a significant opportunity to personalise their care and improve their long-term prognosis.

EDITORIAL & AI STANDARDS

AI tools are used solely to structure and summarise evidence from peer-reviewed primary sources. No AI-generated conclusions appear in The Life Science Feed without editor verification against the primary source.

REFERENCES

1. 1. Akhtar MM, et al. Clinical Phenotypes and Prognosis of Dilated Cardiomyopathy Caused by Truncating Variants in the TTN Gene. Circ Heart Fail. 2020;13(10):e006832. doi:10.1161/CIRCHEARTFAILURE.119.006832
2. 2. de Frutos F, et al. Natural History of MYH7-Related Dilated Cardiomyopathy. J Am Coll Cardiol. 2022;80(15):1447-1461. doi:10.1016/j.jacc.2022.07.023
3. 3. Ling X, et al. Characterization of cardiac involvement in patients with LMNA splice-site mutation-related dilated cardiomyopathy and sudden cardiac death. Front Genet. 2024;14:1291411. doi:10.3389/fgene.2023.1291411
4. 4. Smith ED, et al. Desmoplakin Cardiomyopathy, a Fibrotic and Inflammatory Form of Cardiomyopathy Distinct From Typical Dilated or Arrhythmogenic Right Ventricular Cardiomyopathy. Circulation. 2020;141(23):1872-1884. doi:10.1161/CIRCULATIONAHA.119.044934

LICENCE & RIGHTS

MEDICAL DISCLAIMER

This content is intended for healthcare professionals only and does not constitute medical advice. Clinical decisions must be made by qualified practitioners based on individual patient circumstances.