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Review

Clinical and Prognostic Spectrum of Non-Dilated Left Ventricular Cardiomyopathy: The Role of Genetic Status

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Abstract

Non-dilated left ventricular cardiomyopathy (NDLVC) presents a unique clinical paradox: patients with nearly identical phenotypes can face radically different clinical outcomes. NDLVC has been recently recognized as a distinct dynamic phenotype within the spectrum of non-ischemic cardiomyopathies, linked by a high risk of life-threatening arrhythmias. Recent advances in genetics have overcome clinical phenotyping in prognostic accuracy. Specifically, gene-specific scores have been introduced to guide primary prevention ICD in high-risk gene carriers. On the other hand, while gene-elusive cases present a more favourable arrhythmic profile, their long-term clinical outcome is more challenging to predict. Despite advancements in therapeutic strategies, the heterogeneity of the disease represents an ongoing dilemma for risk stratification and long-term surveillance. This review offers a comprehensive analysis of NDLVC management in clinical practice, highlighting the profound prognostic divergence between genetic (both in actionable and VUS carriers) and gene-elusive cohorts. By synthesizing current evidence, we aim to clarify how genotype–phenotype correlations influence clinical outcomes and to provide a framework for more personalized approaches in the follow-up and treatment of these distinct patient populations. Furthermore, we address the current lack of standardized guidelines specifically tailored to gene-elusive phenotypes. In conclusion, NDLVC management requires a paradigm shift towards a multi-parametric, genotype-directed framework, where cardiac magnetic resonance tissue characterisation and personalized risk scores are essential to optimize sudden cardiac death prevention. Future research must leverage artificial intelligence and polygenic risk scores (PRSs) to integrate multi-parametric clinical-imaging data and refine risk stratification beyond traditional binary models. Concurrently, human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) will be pivotal as a translational platform to clarify VUS pathogenicity, unravel gene-specific arrhythmic mechanisms, and accelerate targeted therapeutic interventions.

Keywords: non-dilated left ventricular cardiomyopathy; genotype; phenotype; genetic testing; arrhythmic risk; cardiac magnetic resonance; cardiomyopathy

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1. Introduction

Formally introduced by the 2023 ESC Guidelines on the management of cardiomyopathies to replace the previous term "hypokinetic non-dilated cardiomyopathy", non-

dilated left ventricular cardiomyopathy (NDLVC) is a distinct clinical entity characterized by non-ischemic left ventricular (LV) scarring or fatty replacement, or by isolated global LV hypokinesia without ventricular dilatation [1]. This novel umbrella term encompasses a heterogeneous spectrum of phenotypes previously labelled as non-dilated cardiomyopathy, arrhythmogenic left ventricular cardiomyopathy (ALVC) or arrhythmogenic cardiomyopathy (ACM), failing to fulfil arrhythmogenic right ventricular cardiomyopathy (ARVC) task force and/or Padua criteria. NDLVC encompasses genetic and acquired aetiologies, as well as idiopathic cases where neither pathogenic genetic variants nor precipitating factors are identifiable. Genetic variants most frequently affect Lamin A-C (*LMNA*), Filamin C (*FLNC*), Desmoplakin (*DSP*), Phospholamban (*PLN*), RNA binding motif protein (*RBM20*) and transmembrane protein 43 (*TMEM* 43), manifesting with variable degrees of myocardial fibrosis and an elevated arrhythmic risk, irrespective of the severity of left ventricular systolic dysfunction (LVSD) [2,3]. Conversely, acquired forms are highly heterogeneous encompassing infectious and post-myocarditic aetiologies; inflammatory and autoimmune conditions—notably cardiac sarcoidosis; other forms related to substance exposure (e.g., alcohol, anthracyclines and catecholamines); peripartum cardiomyopathy (PPCM); and conditions associated with neuromuscular disorders including muscular dystrophies [4]. Reflecting a clinical paradox where distinct pathological entities share a common clinical expression, this etiological heterogeneity mandates a multiparametric approach. Hence, the detection of an NDLVC phenotype should prompt a systematic diagnostic evaluation integrating ECG, multimodality imaging and genetic testing to achieve an accurate etiological diagnosis and tailored therapeutic interventions.

2. Methods

In this literature review, a comprehensive narrative search was performed across PubMed/MEDLINE, Embase, and Google Scholar up to the present. The search strategy combined MeSH terms and free-text keywords covering current and historical NDLVC nomenclature (including hypokinetic non-dilated and left-dominant arrhythmogenic cardiomyopathies). In line with a narrative review approach, study selection prioritized qualitative appraisal and clinical relevance over automated protocols. Eligible publications included longitudinal cohort studies, registries, guidelines, and high-impact reviews focusing on genotype–phenotype correlations, advanced CMR findings, major adverse cardiac events, and gene-specific ICD criteria. Priority was given to peer-reviewed, English-language articles published within the last decade to guarantee the integration of contemporary next-generation sequencing data and modern imaging modalities, whereas meeting abstracts, preprints, and small case series lacking robust longitudinal follow-up data were excluded.

3. Clinical Background

NDLVC is an emerging clinical phenotype encompassing a highly heterogeneous spectrum of genetic, inflammatory, infectious, and systemic aetiologies, which consequently necessitates a thorough etiological characterization to achieve accurate prognostic stratification and tailored therapeutic management. The ECG provides important diagnostic and prognostic information, helping to identify disease stage, stratify arrhythmic risk, and, in selected cases, suggest specific genotype–phenotype associations [5]. Accordingly, annual ambulatory ECG monitoring is recommended to detect ventricular and supraventricular arrhythmias as well as atrioventricular conduction abnormalities, with more frequent surveillance in symptomatic patients. Multimodal imaging plays a pivotal role in the diagnosis and follow-up of patients [1]. Transthoracic echocardiography remains the first-line imaging modality, providing comprehensive assessment of cardiac structure and ventricular function. However, its diagnostic yield is often limited in NDLVC as the predominantly

subepicardial or intramural distribution of myocardial fibrosis may not produce detectable abnormalities in ventricular morphology or function. Advanced techniques, including speckle tracking echocardiography and tissue Doppler imaging, may reveal subtle myocardial dysfunction before overt functional impairment becomes evident. Besides conventional techniques, cardiac magnetic resonance (CMR), with its unique ability to detect early fibrous or fibro-adipose replacement, is crucial for early identification of myocardial abnormalities [6]. Non-ischemic late gadolinium enhancement (LGE), represents a hallmark imaging feature of the disease; indeed, tissue characterization can provide essential clues to the underlying etiology [7], offering additional prognostic value regarding both arrhythmic risk and heart failure severity [8,9]. Beyond CMR, positron emission tomography (PET) is particularly valuable when cardiac sarcoidosis is suspected, whereas endomyocardial biopsy should be reserved for selected patients in whom histopathological evaluation is expected to clarify the diagnosis, particularly when inflammatory or immune-mediated etiologies are considered. Finally, comprehensive genetic testing should be performed in all patients with suspected NDLVC [1], as identification of the underlying genetic substrate may redefine diagnosis, enable cascade family screening, improve risk stratification and support tailored therapeutic strategies.

4. Genotype–Phenotype Relations in NDLVC

Growing evidence demonstrates that harbouring actionable pathogenic or likely pathogenic (P/LP) variants drastically affects clinical outcomes in patients with NDLVC. In a large cohort of non-ischemic dilated cardiomyopathy—a phenotype closely overlapping with NDLVC—Escobar-Lopez et al. showed that actionable variant carriers experienced a significantly higher rate of major adverse cardiovascular events (MACE) (31.7% vs. 19.8%), end-stage heart failure (HF), and malignant ventricular arrhythmias (MVA) compared to genotype-elusive peers [10]. Notably, the clinical course and the likelihood of left ventricular reverse remodeling (LVRR) were heavily dependent on the underlying mutated gene rather than baseline clinical phenotype. Besides influencing long-term clinical outcomes, the underlying genetic background critically shapes both LVRR likelihood and the response to guideline-directed medical therapy (GDMT). Specifically, patients harbouring desmosomal variants exhibited limited LVRR, which was primarily linked to the presence of extensive myocardial fibrosis on CMR, despite milder LV dilation. Conversely, carriers of titin truncating variants (*TTNtv*) typically present with limited fibrosis, resulting into a favourable therapeutic response and frequent, significant LVRR. These data align with a recent cohort study evaluating predictors of disease progression in NDLVC, defined by a ≥10% reduction in LVEF and/or transition to a DCM phenotype [11]. The investigators demonstrated that carriers of a P/LP variant in the so-called *high-risk* genes, namely *LMNA*, *FLNC*, *DSP*, *TMEM43*, *PLN*, and *RBM20* [1], significantly increased the risk of adverse remodeling. Conversely, a negative genetic test was associated with a markedly lower risk of disease progression across all evaluated endpoints [11]. In addition, variants in genes encoding nuclear envelope proteins (e.g., *LMNA*, *RBM20*, and *TMEM43*) exhibit a worse arrhythmic profile compared with other genes. Furthermore, Paldino et al. demonstrated that a genotype-based stratification outperforms canonical clinical criteria in quantifying arrhythmic risk in non-hypertrophic cardiomyopathies, including those with an NDLVC phenotype [12]. Specifically, carriers of *"arrhythmic gene variants"* (such as *LMNA*, *FLNC*, *DSP*, and *PKP2*) faced a significantly higher risk of SCD/MVA compared to *TTN* or sarcomeric variant carriers, irrespective of their baseline phenotype or the degree of LVSD. Finally, these findings underscore that the underlying genetic architecture acts as a critical determinant of long-term arrhythmic risk and heart failure progression in NDLVC/ALVC patients. The detection of these variants shifts risk stratification from a 'one-size-fits-all' phenotypic

assessment to a precise, gene-specific prognostic model that directly guides early, life-saving interventions, including implantable cardioverter–defibrillator (ICD) implantation.

5. Clinical Spectrum of High-Risk NDLVC Genotypes

5.1. DSP Gene

Desmoplakin, encoded by *DSP* on chromosome 6, anchors intermediate filaments to the desmosome. Pathogenic *DSP* variants span a wide phenotypic spectrum overlapping with ARVC, ALVC, and DCM; however, these presentations often fail to fulfil established diagnostic criteria, complicating diagnosis, risk stratification, and patient management [13–16]. Emerging evidence suggests *DSP* cardiomyopathy is a distinct clinical entity characterized by predominant left ventricular involvement, mild systolic dysfunction, a specific CMR fibrosis pattern, high arrhythmic propensity and recurrent myocarditis-like episodes [17]. These acute episodes of myocardial injury, termed "hot phases," manifest with chest pain, elevated enzymes, and non-obstructive coronary arteries. Frequently misdiagnosed as viral myocarditis or MINOCA, comprehensive genetic evaluation is pivotal for timely recognition. In *DSP* cardiomyopathy, LVEF is often preserved or mildly reduced due to the subendocardial sparing of the fibrotic scar. Consequently, CMR is the gold standard for phenotypic characterization, detecting typical subepicardial LGE that often presents as a characteristic ring-like pattern [15,16,18]. While VA risk and clinical phenotype depend on the affected gene, growing evidence suggests they are also modulated by the specific intragenic location of the variant. Specifically, in a study of 170 individuals carrying *DSPtv*, it was demonstrated that nonsense-mediated mRNA decay (NMD)-competent variants, which lead to protein degradation and subsequent haploinsufficiency, are enriched in affected subjects and independently predict an earlier disease onset, a higher VA risk, and worse event-free survival [19]. These recent findings suggest that the specific variant location acts as an independent predictor of MVA and should therefore be routinely factored into future gene-specific arrhythmic risk evaluation and clinical decision-making (see Table 1 for a detailed variant-specific risk overview). In their multinational cohort, Carrick et al. introduced and validated the DSP risk score (www.dsp-risk.com, accessed on 20 August 2026), a novel clinical tool designed to predict sustained VAs in individuals harbouring actionable *DSP* variants [20]. This five-parameter model offers strong discriminatory performance and a practical framework for arrhythmic risk stratification, directly supporting a gene-first approach to patient management.

Table 1. Precision Risk Stratification in NDLVC: Integration of Genotype Architecture, Tissue Phenotypes, and Clinical Red Flags.

Gene	Protein & Pathogenetic Mechanism	CMR LGE Pattern	Clinical Presentation & "Red Flags"	Major Risk (High Penetrance)	Minor Risk (Low Penetrance)
DSP	Desmoplakin NMD-mediated haploinsufficiency and desmosomal instability	Subepicardial, circumferential "ring-like" LGE	Myocarditis-like "hot phases" Chest pain and troponin elevation with non-obstructive coronaries	DSPtv (truncating) in NMD-competent regions	Missense variants C-terminus
LMNA	Lamins A/C Disrupted nuclear integrity, mechanotransduction and gene expression	Linear mid-wall striae in the basal-to-mid septum	Early AV conduction defects and atrial tachyarrhythmias Often precede systolic dysfunction or ventricular dilation	All truncating variants Head/Rod missense (high HF risk)	Tail domain missense (exons 7–12; lower VA/HF rates)

Table 1. *Cont.*

Gene	Protein & Pathogenetic Mechanism	CMR LGE Pattern	Clinical Presentation & "Red Flags"	Major Risk (High Penetrance)	Minor Risk (Low Penetrance)
FLNC tv	Filamin C Haploinsufficiency and sarcolemmal vulnerability	Subepicardial or "ring-like" LGE, mainly inferolateral	Frequent NSVT, syncope and precordial T-wave inversion Mixed DCM/ALVC phenotype	Truncating (FLNCtv) loss-of-function High risk if LVEF <58%.	ROD2 missense (HCM/RCM)
RBM20	RNA-binding protein 20 Exon 9 hotspot missense variants: toxic cytoplasmic accumulation	Variable mid-wall or subepicardial LGE No pathognomonic pattern	Early heart failure Life-threatening VA disproportionate to systolic impairment	Exon 9 hotspot missense (e.g., P638L, R634W)	Truncating variants (RBM20tv) (milder, later onset)
PLN	Phospholamban p.Arg14del founder variant: calcium dysregulation and protein aggregation	Inferolateral subepicardial or circumferential LGE May precede ventricular remodeling	Low QRS voltage and diffuse repolarization abnormalities High PVC burden and sudden death	p.Arg14del deletion (founder mutation; high aggregation)	Standard missense or promoter variants (indolent course)
TMEM43	Transmembrane protein 43 Nucleo-cytoplasmic uncoupling and intercalated disc disruption	Subepicardial inferolateral LGE	Lethal autosomal dominant ARVC5 Early, male-predominant malignant VA, worsened by vigorous exercise	p.S358L missense (malignant ARVC5, males, exercise)	Non-S358L variants (lower association with early SCD)

5.2. LMNA Gene

LMNA encodes lamin A and C, nuclear-envelope proteins involved in nuclear integrity, mechano-transduction and gene regulation [21]. LMNA cardiomyopathy typically present with early-onset electrical disorder before developing myocardial dysfunction [22,23]. LMNA is considered a high-risk gene within the DCM/NDLVC spectrum as malignant ventricular arrhythmias may precede overt dilatation or severe systolic dysfunction [1,24]. CMR typically reveals linear mid-wall fibrosis involving the basal-to-mid interventricular septum, frequently mirroring conduction defects; nonetheless, LGE may be absent in early-stage disease, and its distribution is neither pathognomonic nor mandatory for LMNA cardiomyopathy [25–27]. As clinical trajectories vary by variant class, this criterion was integrated into the LMNA-risk VTA model. In addition, growing evidence suggests that variant location critically influences the natural history of LMNA cardiomyopathy [28–30]. Specifically, truncating or non-missense variants confer a substantially higher risk of malignant ventricular arrhythmias than missense mutations, regardless of their position, whereas the impact on heart failure risk appears more nuanced. Recent data identify missense variants within the head or rod domains as independent predictors of advanced heart-failure events. Conversely, those within the tail domain, particularly if encoded by exons [26–31], are associated with lower rates of both ventricular arrhythmias and advanced heart failure, whereas rod-domain missense variants exhibit a heart failure risk comparable to truncating variants [31,32]. Therefore, a simple missense/non-missense classification may conceal clinically relevant topological heterogeneity. Thus, LVEF alone inadequately reflects the dual risk of sudden death and disease progression. Rather, a comprehensive approach integrating variant class, location, conduction defects, NSVT,

LVEF, and myocardial fibrosis is essential to guide surveillance, primary-prevention ICD considerations and timely referral for advanced heart-failure evaluation.

5.3. FLNC Gene

Filamin C is a structural protein essential for sarcomeric stability and myocardial mechanosignaling, consisting of an N-terminal actin-binding domain, 24 Ig-like repeats (ROD1 and ROD2), and a C-terminal dimerization domain [33]. Pathogenic variants in *FLNC* represent an emerging and clinically relevant cause of hereditary cardiomyopathy, accounting for an estimated 1% to 8% of cases across several phenotypes [34]. Among these, truncating variants (*FLNCtv*) drive the NDLVC phenotype through haploinsufficiency, disrupting cytoskeletal integrity. The resulting vulnerability to physical stress promotes non-ischemic fibrosis, typically manifesting as a characteristic subepicardial or circumferential 'ring-like' LGE pattern on CMR [33,35]. Conversely, ROD2-clustered missense mutations alter protein folding and form toxic intracellular aggregates, predominantly resulting in hypertrophic or restrictive cardiomyopathy phenotypes. Ortiz-Genga et al. first described *FLNC*-related CMP as an overlap phenotype between DCM and LDAC. This entity features mild left ventricular dilation and systolic dysfunction, predominantly subepicardial fibrosis and a high incidence of VAs and SCD [35]. Subsequently, Gigli et al. comprehensively defined this clinical phenotype and its natural history by analysing an international registry of 85 patients with *FLNC*tv [36]. Phenotypic presentation varied across DCM (36–49%), ALVC (17–25%), and ARVC (3%). Nonetheless, a high-risk arrhythmogenic profile was universal, frequently featuring NSVT (48%), syncope (22%), precordial TWI (~20%), and left ventricular inferolateral subepicardial LGE at CMR. Data from the largest *FLNC*tv cohort ($n = 308$) reinforced these findings, showing a 4% annual SCD/MVA incidence, mostly clustered among probands and phenotype-positive subjects [37]. Multivariable analysis identified five independent arrhythmic predictors: age, male sex, syncope, NSVT, and LVEF. Crucially, LVEF displayed a non-linear relationship with risk: values >58% were highly protective, but risk did not increase progressively below this threshold, directly challenging the conventional <45% threshold proposed by consensus guidelines. Based on these five variables, the authors developed a quantitative risk stratification algorithm with good internal discrimination to optimize personalized management. Despite lacking external validation, this tool can guide primary-prevention ICD indications and phenotype-negative relatives' management, though it should be integrated into a multiparametric assessment alongside conventional criteria (LVEF and LGE pattern).

5.4. RBM20 Gene

RBM20 encodes an RNA-binding protein that acts as a cardiac splicing regulator for several genes involved in myocardial structure, contractility and calcium handling, most notably *TTN* [38]. RBM20 cardiomyopathy commonly manifests as early-onset DCM or NDLVC, characterized by a high long-term risk of heart failure and ventricular arrhythmias that may occur out of proportion to underlying systolic disfunction [39,40]. LGE presents variably as mid-wall or subepicardial, though no specific CMR signature has been established [41]. Notably, allelic heterogeneity reflects distinct molecular pathways and clinical outcomes. Missense variants within exon 9 hotspots, specifically the RS domain, cause impaired phosphorylation, leading to RBM20 cytoplasmic mislocalization and aberrant ribonucleoprotein aggregation [42–45]. These variants, by combining loss of nuclear splicing activity and a toxic cytoplasmic gain of function, correlate with earlier, highly penetrant and frequently arrhythmogenic disease [46,47]. Conversely, truncating variants primarily cause loss of function, lacking the toxic effects of protein mislocalization [48,49]. Recent

data confirm their pathogenicity in DCM/NDLVC but indicate a later onset, milder initial presentation, and better outcomes compared to hotspot missense variants.

5.5. PLN Gene

Phospholamban, encoded by *PLN*, is a sarcoplasmic reticulum protein that modulates cardiomyocyte contractility, relaxation, and calcium reuptake via SERCA2a inhibition [50,51]. *PLN* cardiomyopathy is best characterized for the founder p.Arg14del variant, particularly prevalent in the northern Netherlands but identified worldwide, which disrupts calcium homeostasis and promotes pathological phospholamban aggregation [52]. Carriers develop an age-dependent DCM/NDLVC–arrhythmogenic overlap, often characterized by low QRS voltages, repolarization abnormalities, frequent ventricular ectopy and malignant ventricular arrhythmias [53]. LGE with an inferolateral subepicardial or ring-like pattern may be present on CMR and precede ventricular dilatation or systolic dysfunction [54]. Major cardiac-event penetrance approaches 70% by 70 years of age, although expression remains highly variable [55]. A validated p.Arg14del-specific model combines LVEF, PVC burden, T-wave inversion and low-voltage ECG to estimate five-year major ventricular arrhythmia risk and retains discriminatory value when reassessed longitudinally, supporting individualized ICD consideration [56,57].

5.6. TMEM43 Gene

Transmembrane protein 43 (TMEM43, also known as LUMA)is a highly conserved protein in the nuclear membrane and intercalated discs, maintaining mechanical stability and electrical propagation. Pathogenic variants disrupt nucleo-cytoplasmic linkage, mechanotransduction, and cell junction assembly, creating an arrhythmogenic substrate prior to overt ventricular dysfunction [58,59]. *TMEM43*-related CMP is characterized by an autosomal dominant, highly penetrant and particularly malignant form of arrhythmogenic cardiomyopathy known as ARVC5, first reported in 2008 as a distinct clinical entity secondary to the pathogenic p.S358L founder variant [60]. Carriers typically present with early-onset, male-predominant MVA, sustained VT, and SCD. Beyond classic ARVC, TMEM43 mutations can manifest as a left-dominant phenotype. Matos et al. reported LVSD in 57% of patients and subepicardial LGE in 78% (mostly inferolateral), which correlates with high arrhythmic risk and perfectly mirrors NDLVC criteria [61,62]. Basso et al. reported a left-dominant phenotype in their cohort, though less frequently than in *FLNC*- or *DES*-related cases, exhibiting marked intrafamilial heterogeneity and incomplete penetrance [63]. These findings, along with its restricted geographical distribution, support *TMEM43* as an endemic gene whose full arrhythmogenic phenotype likely requires additional genetic and epigenetic modifiers to drive individual susceptibility. Due to its highly malignant profile, *TMEM43* is classified as a high-risk gene by the ETF, warranting primary-prevention ICD consideration if additional risk factors coexist [1]. Finally, emerging therapeutic strategies, particularly AAV-mediated TMEM43 wild-type supplementation, have shown the ability to restore nuclear integrity and attenuate disease progression, positioning TMEM43 as a promising target for future gene-based interventions in ACM [64].

6. Gene-Elusive and VUS Phenotypes

6.1. The Gene-Elusive Cohort

Patients with NDLVC and a negative genetic test represent a highly heterogeneous cohort, spanning acquired conditions and a residual, idiopathic subset where no underlying trigger is identified despite a comprehensive work-up. Idiopathic NDLVC must be distinguished from acquired forms (so called *phenocopies*) driven by heterogeneous pathological triggers, including post-infectious myocarditis, cardiotoxicity induced by chemotherapeutic

agents, substance abuse, or chronic alcohol consumption, tachyarrhythmia-induced cardiomyopathy (TICM), systemic immune-mediated conditions, namely cardiac sarcoidosis (CS) and peripartum cardiomyopathy (PPCM) [4]. Such phenocopies may share overlapping features with monogenic cardiomyopathies, making differential diagnosis extremely challenging. Specifically, the myocardial scarring resulting from chronic myocarditis or cardiac sarcoidosis can closely replicate the LGE distribution seen in *DSP* or *FLNC* variant carriers. An integrated, multidisciplinary evaluation systematically including genetic screening is essential to accurately distinguish between these entities, thereby preventing misclassification and subsequent suboptimal clinical management. Recent multicenter data suggest that gene-elusive NDLVC patients exhibit a more favourable disease course. Evaluating a cohort of 432 patients followed for a median of 77 months, *Bacigalupi* et al. demonstrated that gene-elusive status independently predicted a lower risk of adverse remodelling to DCM. Instead, adverse remodelling was independently predicted by a cluster of factors including positive genetic testing associated with myocardial inflammation, family history of cardiomyopathy or sudden cardiac death, intraventricular conduction delay, baseline LVEF $< 45\%$, and a ring-like LGE pattern on CMR [11]. These data support genotype-negative status as a favourable prognostic marker, while confirming that "gene-elusive" is not synonymous with "risk-free," particularly when inflammatory activity or high-risk imaging markers coexist. The clinical management of gene-elusive patients relies inherently on a phenotype-driven approach. In the absence of a defining genetic substrate, risk stratification is guided by longitudinal monitoring of left ventricular ejection fraction, arrhythmic burden via Holter ECG, and the extent of myocardial fibrosis on CMR. The newly developed NDLVC-5y score represents a crucial advancement in the management of NDLVC, offering an individualized estimation of 5-year arrhythmic risk. This multi-parametric risk calculator refines primary prevention strategies by integrating conventional clinical markers, such as sex and left ventricular ejection fraction, with advanced imaging findings (septal and ring-like late gadolinium enhancement), documented non-sustained ventricular tachycardia, genetic background, and tissue-proven myocardial inflammation [65]. This score is very useful in gene-elusive cohort since it allows for a tailored clinical approach; indeed, by evaluating clinical data together with specific CMR imaging features it provides accurate arrhythmic risk stratification despite the lack of genetic data. Beyond individual risk assessment, this score refines familial surveillance strategies, tailoring the intensity of longitudinal cardiological follow-up based on the phenotypic severity displayed by the proband. Finally, second- and third-line genetic testing is not routinely performed but is indicated in specific clinical and familial scenarios. In cases presenting with syndromic features or a family history highly suggestive of mendelian inheritance, whole-exome or whole-genome sequencing (WES/WGS) should be considered. Conversely, when the clinical phenotype strongly points toward a specific pathology, targeted screening for large structural rearrangements via Multiplex Ligation-dependent Probe Amplification (MLPA) is warranted. This approach is essential to evaluate copy number variations in key genes such as *DSP*, *PKP2*, or *DMD*, where macrodeletions represent an established cause of disease [66,67].

6.2. The Variant of Uncertain Significance (VUS) Carriers

Since NDLVC represents a novel clinical entity, its genetic diagnostic yield has yet to be fully established. Nonetheless, even with comprehensive next-generation sequencing (NGS) panels, the detection rate of actionable Mendelian variants across inherited cardiomyopathies remains low, falling below 30% in DCM [10,68,69] and accounting for approximately two-thirds of ACM cases [70]. A negative genetic result in a proband does not rule out a hereditary disorder but rather underscores our current limitations in under-

standing the genetic architecture of inherited cardiomyopathies. To standardize evaluation, laboratories implement strict clinical genomic where variant classification integrates phenotypic, epidemiological, population-based and computational data, culminating in a five-tier classification framework: benign (B), likely benign (LB), variants of uncertain significance (VUS), likely pathogenic (LP), and pathogenic (P) [71,72]. Where there is conflicting or insufficient evidence, the variant is classified as a variant of uncertain significance (VUS), representing an estimated probability of pathogenicity between 10% and 90%. To help reduce the gap between clinical ambiguity and definitive diagnosis, VUSs have recently been stratified along a continuous spectrum from 'cold'—likely benign—to 'hot' alleles. This sub-classification is strictly grounded on the cumulative weight of key multi-parametric data, including population allele frequencies in gnomAD, consensual in silico pathogenicity predictors, familial co-segregation patterns, and predicted structural or functional impacts on cardiac proteins [73]. VUS findings often challenge post-test counselling, as they are strongly linked to increased patient anxiety, misinterpretation of results, and suboptimal engagement in family screening cascades [74,75]. Retrospective studies report no clinical divergence between VUS carriers and patients with actionable variants. However, P or LP mutations consistently correlate with worse long-term outcomes and major adverse events, indicating that VUS alone are insufficient to drive pathogenesis within a multigenic and multifactorial disease background [76,77]. Further complicating this scenario, the widespread adoption of expansive multigene panels, whole-exome sequencing (WES), and whole-genome sequencing (WGS) along with testing in borderline phenotypes, has dramatically increased VUS frequency [78,79]. Considering the prevalence of rare, benign variants in healthy genomes, a VUS represents an indeterminate finding that cannot guide clinical decision-making or cascade screening [80]. Instead, a family segregation study can be performed to ascertain whether the same variant tracks with the disease phenotype within the pedigree, distinguishing de novo events from inherited alleles. While not a diagnostic test per se, its primary goal lies in gathering sufficient evidence to facilitate the reclassification of the VUS toward either a benign or LP/P status. Therefore, rather than establishing a diagnosis, a VUS represents a dynamic, evidence-dependent finding that underscores the current limitations of medical knowledge and the complexity of interpreting genomic variation. The clinical relevance of a variant can only be properly assessed within the broader context of the patient's phenotype, family history, and diagnostic evaluation. Figure 1 provides a comprehensive flowchart illustrating the systematic management and interpretation of VUS, alongside their direct clinical impact on both the proband and family members. Therefore, multidisciplinary collaboration between geneticists and cardiologists is essential to mitigate clinical uncertainty, a goal achieved through detailed phenotypic characterization, family-based studies, and continuous genetic data driven by familial segregation and functional assays [81,82]. Since a variant may eventually prove pathogenic as novel cases are documented and additional data accumulate, comprehensively addressing the implications of VUS detection constitutes a mandatory component of pre-test genetic counselling. Finally, the primary challenge of contemporary genomic medicine is no longer variant identification, but rather discerning which one truly matters.

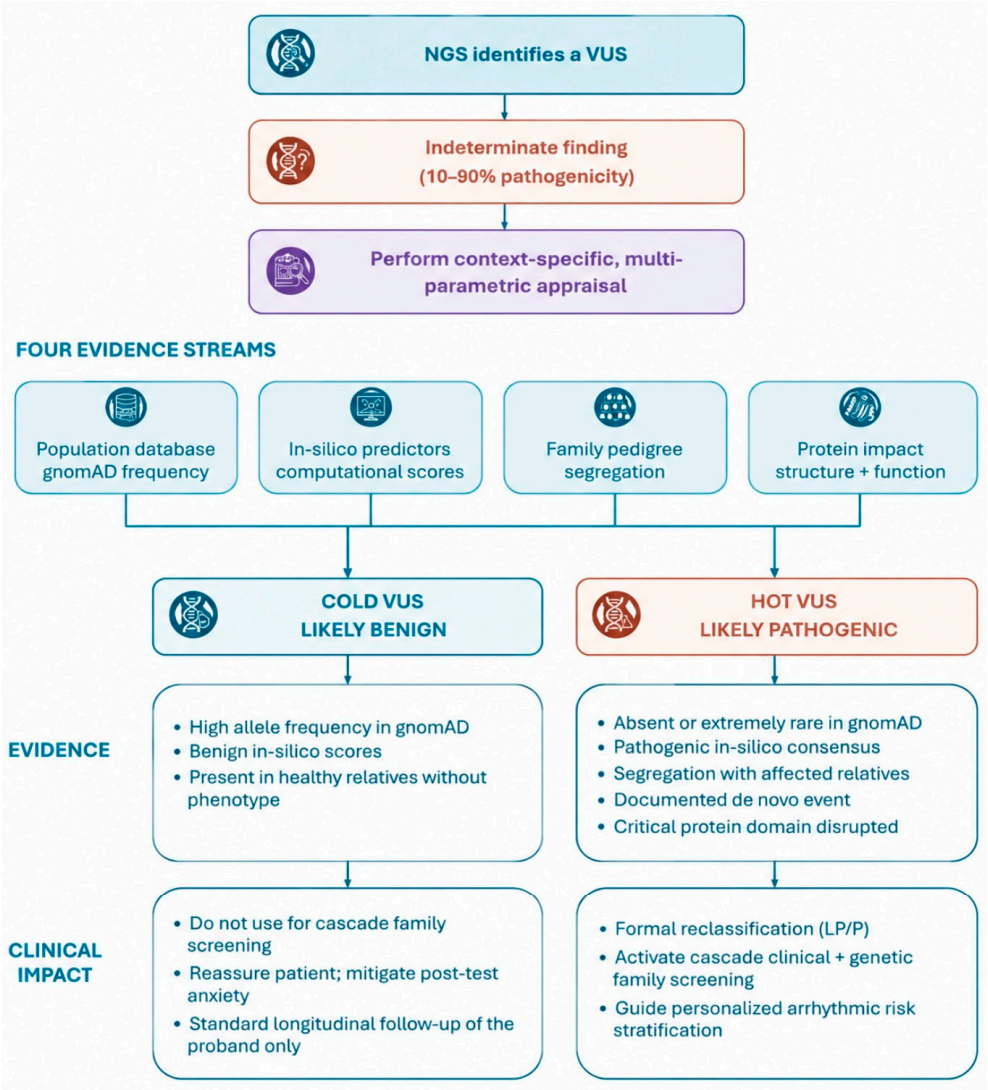


Figure 1. Methodological Workflow for VUS Management: From Multi-Parametric Evidence Streams to Clinical Decision-Making.

7. Clinical Management and Therapeutic Strategies

Preventing SCD is a cornerstone in the management of patients with NDLVC. While a LVEF of 35% or less has traditionally served as the primary criterion for prophylactic ICD implantation, genetic background has emerged as a major determinant of arrhythmic risk in this cohort [1]. In particular, patients carrying variants in genes linked to a high arrhythmic potential, namely *LMNA*, *FLNC*(tv), *TMEM43*, *RBM20*, *PLN*, and *DSP*, exhibit a substantially higher incidence of major arrhythmic events compared with other genetic subgroups, independently of LVEF. Growing evidence on cardiomyopathies suggest to consider primary prevention ICD implantation with a class IIa recommendation, irrespective of LVEF, when additional risk factors are present, including a history of unexplained syncope and the presence of LGE on CMR [1]. Moreover, for specific high-risk genes, including LMNA, DSP, and PLN, genotype-specific predictive risk models have been developed and validated [37]. When available, these tools should be integrated into clinical decision-making to refine arrhythmic risk assessment and guide primary prevention ICD implantation [1]. The 2017 ACC/AHA/HRS guidelines on ventricular arrhythmias provided specific recommendations for ICD implantation in *LMNA*-related non-ischemic cardiomyopathy, including criteria such as LVEF <45%, male sex, and NSVT [83]. Similarly, the 2022 ESC guidelines for the management of ventricular arrhythmias and the prevention of SCD grants a class

IIa ICD indication to patients with dilated or hypokinetic non-dilated cardiomyopathy (DCM/HNDCM) and *LMNA* variants who present a ≥10% estimated 5-year risk of VA (https://lmna-riskvta.fr/, accessed on 20 August 2026) and either LVEF < 50%, NSVT, or atrioventricular conduction delay [84]. Furthermore, a class IIa indication is extended to DCM/HNDCM patients with LVEF between 36 and 50% and at least two additional risk factors, including unexplained syncope, pathogenic variants in *PLN*, *FLNC*, or *RBM20*, LGE on CMR, or inducible sustained monomorphic VT (SMVT) during electrophysiological study (EPS). Limited data are currently available to guide risk stratification in patients without an identified causative gene variant. Given that most sudden cardiac deaths occur in patients with preserved or mildly reduced LVEF, the Task Force suggests that primary preventative ICD implantation may be considered in selected patients with additional risk markers, such as NSVT, a family history of SCD or significant LGE on CMR (Table 2). However, there are no RCTs available exploring the usefulness of primary prevention [85]. The presence, extent and distribution of non-ischemic myocardial fibrosis, constitute the strongest predictor of MVA, identifying a high risk subgroup [86]. In patients with unexplained syncope, programmed electrical stimulation (PES) may offer additional insights into the underlying cause [87]. Inducibility of SMVT at PES was included as an additional risk factor in the 2022 ESC GL for the management of patients with VA and prevention of SCD [84], but not reported in the 2023 ESC Guidelines on cardiomyopathies. Definitive data supporting the routine use of PES for primary prevention risk stratification are currently lacking, and its role in clinical decision-making remains uncertain. A more personalized framework for the management, therapeutic strategy, and follow-up of NDLVC patients and their relatives, guided by genetic status, is illustrated in Figure 2.

Table 2. Schematic Overview of contemporary ICD indications in NDLVC: an integrated approach based on LVEF, risk calculators and risk modifiers.

Domain	Actionable Genetic Cohort (P/LP)	VUS Cohort (Uncertain Significance)	Gene-Elusive Cohort (Genotype-Negative)
Arrhythmic Risk Profile	High arrhythmic risk Often independent of LVEF thresholds	Unpredictable, variable risk Ongoing clinical reassessment and variant tracking	Generally more favorable risk Long-term heterogeneity limits prediction
Guideline Applicability	Validated gene-specific risk scores Established consensus criteria	Partial, non-specific guidance Empirical, phenotype-based management	Limited or absent guidance Lack of standardized long-term surveillance
Future Role of Polygenic Risk Scores (PRS)	Penetrance modification Prediction of earlier onset or greater fibrosis	Polygenic susceptibility assessment Support for variant reclassification	Detection of occult oligogenic/polygenic substrates Predisposition to progressive failure
Translational hiPSC-CM Modeling	In vitro modeling with CRISPR/Cas9 Pathway mapping and causal validation	Gold standard for variant validation Confirmation or exclusion of pathogenicity	Non-coding genetic vs acquired etiologies In vitro disease phenotype assessment
Future Artificial Intelligence (AI) Integration	Refined ICD implantation timing Integration of genomic scores and imaging	Prediction of variant stability over time Modeling of tracking parameters	Detection of subclinical voxel-level strain changes Identification of concealed ECG repolarization anomalies

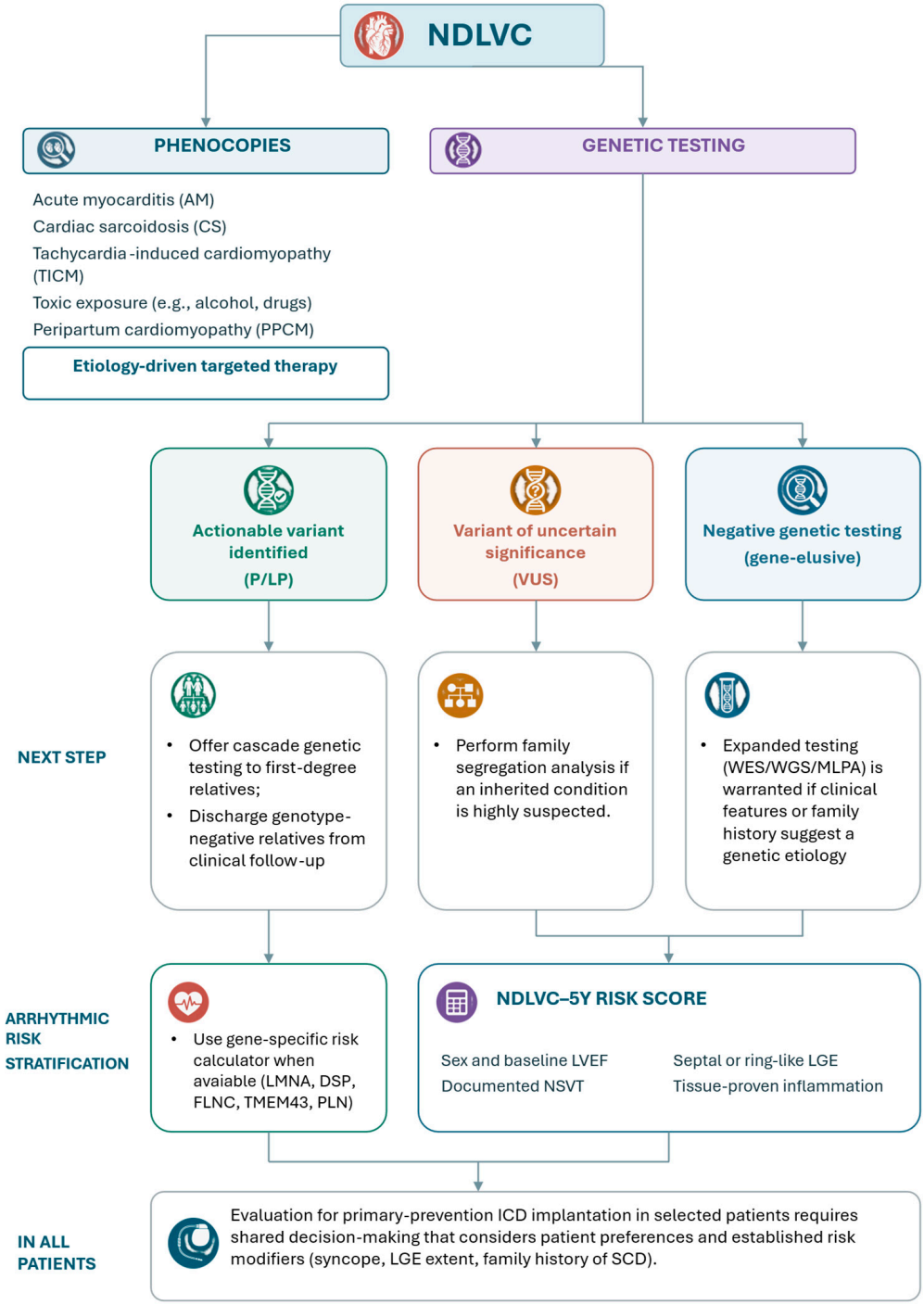


Figure 2. Role of genetic testing in patient stratification and integrated diagnostic workflow for suspected NDLVC: from phenotype to aetiological diagnosis and personalized management.

8. Discussion

The formal classification of NDLVC by the ETF represents a paradigm shift, unifying diverse non-ischemic conditions under a single, actionable umbrella phenotype rather than a distinct clinical entity, encompassing a highly sophisticated and heterogeneous etiological architecture. The diagnostic workup in NDLVC requires a structured, multiparametric workflow. While echocardiography remains the first-line diagnostic tool, it frequently misses early abnormalities, so that CMR has become the gold standard imaging modality, providing critical tissue characterization through specific LGE patterns. Identifying pathogenic variants in NDLVC shifts clinical management from a "one-size-fits-all" phenotypic evaluation

toward a genotype-specific risk model, bypassing traditional LVEF thresholds. Despite a more favourable prognosis, gene-elusive patients retain a non-negligible residual risk when active myocardial inflammation or structural scarring is present, necessitating rigorous, longitudinal surveillance. In this setting, the NDLVC 5-Y score serves as a valuable tool to accurately quantify this residual arrhythmic risk and guide personalized clinical follow-up. Furthermore, VUS carriers represent a unique challenge due to the absence of standardized, disease-specific management and follow-up protocols. In this uncertain scenario, the interpretation of a VUS cannot rely on laboratory data alone but it requires a meticulous context-specific appraisal integrating the family pedigree, cascade co-segregation studies, and the individual clinical-imaging phenotype. The widespread adoption of large NGS panels, WES and WGS, has drastically increased VUS frequency, particularly among patients with borderline phenotypes; thus, careful test selection is paramount to preserve specificity, as expanding genetic panels significantly amplifies VUS detection for only a minor incremental yield in actionable variants. Deepening our understanding of these intermediate phenotypes is an absolute priority to optimize long-term surveillance, balancing adequate protection with the prevention of unnecessary psychological burden. Finally, although identifying an actionable variant critically shapes diagnosis and prognosis, this finding alone cannot definitively predict the natural history and disease evolution, given that the same variant can lead to highly divergent clinical presentations. Such phenotypic heterogeneity emphasizes the necessity of integrating genetic findings within a comprehensive framework of clinical, imaging, and environmental parameters.

9. Gaps in Knowledge and Future Perspectives

Despite rapid advances, the biological architecture of NDLVC remains far from fully understood. Future research should move beyond a binary gene-carrier/gene-elusive classification and distinguish "true" from "false" gene-elusive cases, in which current testing fails to capture the layered contribution of rare variants, oligogenic or recessive inheritance, copy number variations, non-coding variation, polygenic susceptibility, epigenetic regulation and environmental triggers [3,88–91]. Notably, although polygenic risk assessment remains distant from routine clinical application, it may offer a valuable means of exploring the genetic background of apparently gene-elusive disease and revealing susceptibility not captured by conventional testing [92]. By aggregating hundreds of common, small-effect single-nucleotide polymorphisms, Polygenic Risk Scores (PRSs) can refine risk stratification across distinct cohorts. In genotype-positive patients harboring high-risk monogenic variants (e.g., DSP or FLNC), a high background polygenic burden acts as a phenotypic catalyst that accelerates disease onset, promotes adverse left ventricular remodeling, and increases CMR-detected myocardial fibrosis [93,94]. Conversely, in traditionally enigmatic gene-elusive cohorts, quantifying this polygenic substrate offers a novel paradigm to identify individuals who, despite a benign initial presentation, carry a higher propensity for progressive LVSD or MVA due to oligogenic or polygenic architectures. Simultaneously, exploring non-coding variations reveals regulatory infrastructures missed by standard exonic panels. Deep intronic variants can introduce cryptic splice sites and pseudo-exons leading to truncated structural proteins—mutations in giant genes like TTN or DSP that are increasingly linked to unexplained arrhythmogenic phenotypes [95]. Furthermore, in both genotype-positive and gene-elusive NDLVC, patient-specific hiPSC-CMs serve as a powerful translational platform to functionalize VUSs and differentiate multi-factorial genetic substrates from acquired, environmental triggers [96,97]. However, despite their profound diagnostic potential to bridge the gap between genotype and phenotype, the translation of these models into routine clinical decision-making remains constrained by the structural and electrophysiological immaturity inherent to their fetal-like state [98].

Alongside advanced genetics, the integration of artificial intelligence (AI) frameworks represents a transformative avenue for risk stratification, particularly within gene-elusive NDLVC cohorts. Deep learning algorithms trained on digital electrocardiogram (ECG) analysis can detect subclinical electrical remodeling and cryptic arrhythmic substrates before they manifest clinically [99,100]. When combined with cardiac magnetic resonance (CMR) tissue tracking, AI-driven radiomics can uncover subtle alterations in myocardial deformation, strain dynamics, and microscopic fibrosis patterns that bypass conventional visual assessment. By synergistically processing these multi-parametric imaging and electrophysiological phenotypes, AI models hold the potential to predict major adverse cardiac events in patients lacking identifiable genetic mutations, paving the way for data-driven, genotype-independent precision monitoring [101,102]. Resolving these uncertainties will require large, multicentre, longitudinal registries integrating deep phenotyping, serial imaging, whole-genome sequencing, and multi-omics profiling across disease stages and diverse populations. Such efforts may ultimately redefine disease taxonomy, uncover hidden mechanisms, and translate biological complexity into more individualized surveillance and risk-stratification strategies.

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Abbreviations

ACM, arrhythmogenic cardiomyopathy; ALVC, arrhythmogenic left ventricular cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; AAV, adeno-associated virus; AUC, area under the curve; CMR, cardiovascular magnetic resonance; CMP, cardiomyopathy; DCM, dilated cardiomyopathy; ECG, electrocardiogram; FLNCtv, FLNC truncating variants; GDMT, guideline-directed medical therapy; HF, heart failure; ICD, implantable cardioverter–defibrillator; LGE, late gadolinium enhancement; LP, likely pathogenic; LVEF, left ventricular ejection fraction; LVRR, left ventricular reverse remodeling; LVSD, left ventricular systolic dysfunction; MACE, major adverse cardiovascular events; MINOCA, myocardial infarction with non-obstructive coronary arteries; MLPA, Multiplex Ligation-dependent Probe Amplification, MVA, malignant ventricular arrhythmias; NDLVC, non-dilated left ventricular cardiomyopathy; NGS, next-generation sequencing; NIDCM, non-ischemic dilated cardiomyopathy; NMD, nonsense-mediated mRNA decay; NSVT, non-sustained ventricular tachycardia; P, pathogenic; P/LP, pathogenic/likely pathogenic; PES, programmed electrical stimulation; PET, positron emission tomography; PLN, phospholamban; PVC, premature ventricular contractions; RBM20, RNA-binding motif protein 20; SCD, sudden cardiac death; TTNtv, titin truncating variants; TWI, T-wave inversion; VA, ventricular arrhythmias; VTA, ventricular tachyarrhythmias; VUS, variant of uncertain significance; WES, whole-exome sequencing; WGS, whole-genome sequenc-

ing; ACMG, American College of Medical Genetics and Genomics; AMP, Association for Molecular Pathology; DSP, desmoplakin; gnomAD, Genome Aggregation Database; RV, right ventricular; VE, ventricular ectopic beats; LMNA, lamin A/C;TMEM43, transmembrane protein 43.

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