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Precision medicine applications in dilated cardiomyopathy: Advancing personalized care

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ABSTRACT

Dilated cardiomyopathy (DCM) is a prevalent cardiac disorder affecting 1 in 250–500 individuals, characterized by ventricular dilation and impaired systolic function, leading to heart failure and increased mortality, including sudden cardiac death. DCM arises from genetic and environmental factors, such as drug-induced, inflammatory, and viral causes, resulting in diverse yet overlapping phenotypes. Advances in precision medicine are revolutionizing DCM management by leveraging genetic and molecular profiling for tailored diagnostic and therapeutic approaches. This review highlights comprehensive diagnostic evaluations, genetic discoveries, and multi-omics approaches integrating genomic, transcriptomic, proteomic, and metabolomic data to enhance understanding of DCM pathophysiology. Innovative risk stratification methods, including machine learning, are improving predictions of disease progression. Despite these advancements, the current one-size-fits-all management strategy contributes to persistently high morbidity and mortality. Emerging targeted therapies, such as CRISPR/Cas9 genome editing, aetiology-specific interventions, and pharmacogenomics, are reshaping treatment paradigms. Precision medicine holds promise for optimizing DCM diagnosis, treatment, and outcomes, aiming to reduce the burden of this debilitating condition.

Introduction

Dilated cardiomyopathy (DCM) is an umbrella term encompassing a wide range of genetic and non-genetic etiologies that lead to left ventricular (LV) dysfunction and dilation of non-ischemic origin.[1] DCM is the most common indication for heart transplantation and the third most common cause of heart failure (HF).[2] Its prevalence is estimated to be about 1:250-1:500 in the general population, and it seems to be slightly higher in men.[3,4] Familial DCM has been reported to explain 30-50 % of cases, while a gene is identified in 20–35 % of those.[5,6] The clinical presentation of DCM can vary widely, ranging from asymptomatic cases to severe HF symptoms or sudden cardiac death (SCD).[7] Over the past twenty years, significant advancements have been made in understanding the complex genetic underpinnings of DCM. Comprehensive clinical evaluations of DCM patients, thorough family screenings, and the use of advanced imaging techniques have enabled earlier and more accurate diagnoses, as well as more specific criteria for implantable

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cardioverter defibrillator (ICD) implantation to prevent SCD. In the context of precision medicine, therapies tailored to specific genetic mutations are beginning to develop.

DCM is characterized by LV diffuse contractile dysfunction and dilatation, occurring independently of abnormal loading conditions such as hypertension, valvulopathies, or coronary artery disease (CAD).[8] It is a progressive disease with poor prognosis, and it is characterized by repeated exacerbations and hospitalizations due to advanced HF.[9] Diagnosis is established by an LV end-diastolic diameter (LVEDD) exceeding 2 standard deviations (SD) from the predicted values, along with LV fractional shortening <25 % or an LV ejection fraction (EF) below 45 %. Predicted values are determined using Henry's formula, adjusted for age and body surface area, and presented as a percentage of the predicted diameter. Specifically, the predicted LVEDD is calculated as follows: Predicted LVEDD = (45.3 × body surface areaˆ0.3) − (0.03 × age) − 7.2. A LVEDD value exceeding 112 % (> 2SD) serves as a diagnostic criterion for DCM, while a value surpassing 117 % (2SD + 5 %) enhances specificity.[10]

Until recently, the management of patients with DCM has primarily revolved around conventional HF treatment strategies, encompassing medication regimens, device therapy, and consideration for heart transplantation when deemed necessary.[11] Nevertheless, it's important to note that the therapy of HF traditionally follows a "one-size-fits-all" approach, highlighting the need for precision and targeted therapies tailored to the individual characteristics of each patient. The prognosis for individuals with DCM has markedly enhanced over the past few decades, attributable to advancements in both pharmacological and non-pharmacological interventions.[8] This improvement is further facilitated by earlier diagnoses stemming from familial screening initiatives and pre-participation cardiac assessments, coupled with personalized long-term monitoring.[12] Consequently, survival rates exceeding 80 % at an 8-year follow-up period, coupled with a reduced necessity for heart transplantation, reflect the substantial progress achieved in managing DCM.[13] However, despite these advancements, there is still increased morbidity and mortality among patients, highlighting the need for further development of targeted and genome-directed therapies.

Precision medicine transforms the management of DCM by tailoring diagnostic and therapeutic strategies to individual genetic and molecular profiles. This review provides an in-depth exploration of the latest advancements in DCM diagnosis, including comprehensive diagnostic workups and cutting-edge genetic insights. Multi-omics approaches that integrate genomic, transcriptomic, proteomic, and metabolomic data try to offer a holistic understanding of DCM pathophysiology. Additionally, innovative methods for risk stratification and prognostication enhance the ability to predict disease progression and outcomes. Targeted therapies, such as precise genome editing with CRISPR/Cas9, and etiology-specific interventions, are highlighted for their potential to transform DCM treatment paradigms. This review underscores the promise of precision medicine in improving the diagnosis, management, and therapeutic outcomes for patients with DCM.

Pathogenesis and etiology of DCM

Various genetic and acquired causes of LV dysfunction can present with the same clinical phenotype of DCM.[14] According to the ESC classification of cardiomyopathies, DCM is categorized into two main types: genetic or acquired.[11] Approximately 20-40 % of DCM cases are familial, resulting from inherited genetic mutations.[15] Mutations in genes encoding sarcomeric proteins (e.g., MYH7, TNNT2), cytoskeletal proteins (e.g., DES, DMD), and ion channel proteins (e.g., SCN5A) are commonly implicated.[16] These genetic abnormalities disrupt myocardial structure and function, predisposing individuals to DCM. However, phenotypic expressions vary depending on environmental stressors or different pathogenic variants in individuals. Often, genetic predisposition combined with environmental factors leads to the manifestation of the disorder's phenotype. Several drugs and toxins, including alcohol and antineoplastic drugs like anthracyclines, can directly damage the myocardium, causing LV dysfunction.[17] Alcohol's impact on the heart is dose-dependent, with abstinence potentially reversing LV systolic dysfunction. In contrast, anthracycline treatment typically results in permanent cardiotoxic effects.[18] An inflammatory response causing LV dysfunction, and a DCM phenotype can result from infectious agents (such as viral or bacterial myocarditis), autoimmune disorders (like sarcoidosis), toxic agents (such as cocaine), or other factors.[19,20] Deficiencies in essential nutrients, such as thiamine (beriberi), selenium (Keshan disease), and carnitine, can impair myocardial function and structure, resulting in DCM.[21,22] These deficiencies interfere with energy production and myocardial metabolism. Myocarditis progresses to DCM in up to 30 % of cases, and nearly half of DCM cases show evidence of myocardial inflammation.[14,23] Peripartum cardiomyopathy (PPCM) is a rare and potentially life-threatening condition where HF occurs in the last trimester of pregnancy or within the first few months postpartum.[24]

Diagnosis

DCM exhibits variable phenotypic expressions and age-dependent penetrance, often resulting in patients displaying intermediate phenotypes that do not fully meet standard diagnostic criteria.[11] Advanced imaging techniques such as cardiac magnetic resonance (CMR) have altered the diagnosis and management of DCM by enabling the identification of subtle or extensive myocardial scar even in patients with normal LV dimensions and function.[25] This capability is particularly crucial as significant ventricular arrhythmias (VAs) and SCD may precede any evident structural or morphological changes in the heart.[26] A systematic approach is essential for identifying and managing the diverse range of disorders leading to DCM. Diagnostic workup, therapeutic management, and follow-up require a multifactorial process. Basic evaluation should include personal and family history, physical examination, ECG, cardiac imaging, and laboratory testing. Disease-specific diagnostic clues should guide further diagnostic workup, which may include CMR, endomyocardial biopsy (EMB), and genetic testing.[11] For suspected storage or metabolic diseases, EMB may also be considered. Secondary etiologies like CAD should always be excluded, particularly in patients over 35 or those with a family history of early CAD or significant risk factors.[27]

ECG abnormalities are common in DCM, reported in up to 80 % of patients. Specific ECG phenotypes are associated with certain genetic or acquired forms of DCM.[28] For instance, sinus node disease, AV conduction defects, and marked bradycardia are common in lamin A/C (LMNA) and sodium channel protein type 5 subunit alpha (SCN5A) gene variants, while conduction abnormalities are characteristic in the presence of dystrophin (DMD), and desmin (DES) mutations.[29] Low voltage on the ECG, particularly in the limb leads, is typical of Filamin C (FLNC), phospholamban (PLN), and desmoplakin (DSP) variants, and may precede echocardiographic changes. T wave inversion is found in FLNC and DSP carriers. VAs often occur before overt LV dysfunction in carriers of LMNA, FLNC, DES, DSP, and SCN5A variants.[30] A combination of conduction abnormalities and complex VAs strongly suggests an LMNA variant, while a "posterolateral infarction" pattern with pathologic Q waves raises suspicion of muscular dystrophy. Specific ECG characteristics have prognostic value in DCM.[30] QRS fragmentation and T wave alternans have been identified as potential prognostic markers for VAs. Atrial fibrillation (AF) is associated with a worse outcome and may indicate the need for heart transplantation. Left bundle branch block (LBBB), present in about a third of DCM patients, may precede structural changes in the heart and serve as a poor prognostic indicator.[29]

Echocardiography plays a crucial role in diagnosing, monitoring, and screening for DCM. Parameters like LVEF and NYHA functional class serve as independent predictors of outcomes, with low LVEF and higher NYHA classes correlating with increased mortality and need for heart transplantation.[31] LV dilatation is associated with early VAs, while diffuse LV hypokinesia and eccentric hypertrophy are typical findings. Distinguishing regional wall motion abnormalities from those due to CAD is essential. Diastolic dysfunction, functional mitral regurgitation, and left ventricular reverse remodeling (LVRR) are significant prognostic indicators.[32,33] Right ventricular dilatation and dysfunction also carry prognostic significance, correlating with advanced LV failure. Novel echocardiographic techniques like myocardial strain analysis show promise in detecting early DCM in asymptomatic variant carriers and predicting mortality in symptomatic DCM patients.[34,35]

CMR is invaluable for assessing ventricular size, function, and tissue characterization, particularly in detecting fibrosis through late-gadolinium enhancement (LGE).[36] In DSP disease patients with normal ECG and VAs of left ventricular origin, LGE in LV is the only abnormality detected. Distinct LGE patterns have been observed in patients with pathogenic PLN R14del variants, highlighting differences from other hereditary cardiomyopathies, particularly in the distribution of fibrosis.[37] Novel CMR techniques such as phosphorus P 31 magnetic resonance spectroscopy and diffusion tensor CMR (DT-CMR) provide detailed assessments of myocardial performance, including cardiac energetics and microarchitecture dynamics, potentially offering superior predictive value for mortality compared to traditional metrics like EF.[36] However, the diagnostic and prognostic utility of these methods in early-stage DCM remains to be fully determined.

Circulating biomarkers offer valuable insights into metabolic derangements, collagen turnover, and inflammatory processes, potentially guiding therapy decisions in DCM. While some biomarkers lack cardiac specificity, markers like PICP and PIIINP correlate with cardiac fibrosis and predict unfavorable outcomes in HF patients.[38] Galectin-3 also shows promise as a prognostic marker in DCM due to its association with worse outcomes. Integrating multidimensional data through phenomapping and machine learning approaches helps define distinct subclasses of DCM with shared and unique disease mechanisms, paving the way for more personalized

Table 1
Genetic underpinning in dilated cardiomyopathy.

Gene	Protein	Mutation	Clinical Impact
TTN	Titin	Truncating	Most common mutation 25 % of end-stage disease familial cases (20-25 %) sporadic cases (18 %)
LMNA	Lamin A/C	Missense or truncating	8-10 % Aggressive phenotype Conduction abnormalities Malignant arrhythmias Early ICD placement is recommended
FLNC	Filamin C	Truncating	Arrhythmic DCM without skeletal muscle issues VA, SCD Left-dominant arrhythmogenic cardiomyopathy
BAG3	BCL2-Associated Athanogene 3	Missense or other mutations	High penetrance >40 years old Advanced HF
PLN	Phospholamban	R14del	VA end-stage HF ICD placement
RBM20	Ribonucleic Acid Binding Protein 20	Splicing variant	VA
DES	Desmin	Various mutations	Often associated with muscular dystrophies
DMD	Dystrophin	Truncating	Linked to Duchenne's and Becker's muscular dystrophies
SCN5A	Sodium Channel Protein Type 5 Alpha	Gain-of-function variant	VA Sodium-channel blockers are effective
DSP	Desmoplakin	Truncating	LV fibrosis VA, SCD
TMEM43	Transmembrane Protein 43	p.S358L variant	Males tend to have a worse prognosis

DCM, dilated cardiomyopathy; HF, heart failure; ICD, implantable cardioverter defibrillator; LV, left ventricular; SCD, sudden cardiac death; VA, ventricular arrhythmias.

therapeutic interventions tailored to individual patient subgroups.[8] In DCM patients, elevated levels of diagnostic biomarkers such as BNP, NT-proBNP, and soluble suppression of tumorigenicity 2 (sSt2) have been shown to be strong predictors of adverse prognosis, reflecting both the severity of ventricular dysfunction and the progression of HF.[39,40] Also, biomarkers such as matrix metalloproteinase-2 (MMP-2), tissue inhibitor of metalloproteinase-1 (TIMP-1), growth differentiation factor-15 (GDF-15), and osteopontin (OPN) have demonstrated strong prognostic value, as their increased levels are associated with more severe myocardial remodelling, increased systemic inflammation, and poorer clinical outcomes, highlighting their potential utility in risk stratification and personalized treatment strategies.[41]

Cardiopulmonary Exercise Testing (CPET) is considered as a powerful method in cardiology, especially for determining the prognosis and for risk stratification of heart failure patients, particularly in DCM Patients. All the CPET variables provide synergistic prognostic discrimination. However Peak VO2 serves as the most important parameter for risk stratification and prediction of survival rate. Although an invasive evaluation, based on eg, central oxygen saturation and cardiac output, should be considered in every candidate for LVAD-implantation, CPET is considered as one of the best tools for non-invasive evaluation, due to the fact that can objectively justify and reflect the physical and hemodynamic capacity in rest, but most importantly under exercise.[42,43]

Genetic underpinning insights

Familial cardiomyopathies exhibit diverse inheritance patterns, primarily autosomal dominant but also autosomal recessive, X-linked, and mitochondrial.[44] Causative genes encode proteins crucial for cardiomyocyte function, including Titin (TTN), LMNA, and DSP. DCM arises from mutations, predominantly rare single-nucleotide mutations, within these gene regions, leading to the production of abnormal proteins (Table 1).[1,45] These conditions display significant genetic and allelic heterogeneity, meaning many variants in different genes can cause the same phenotype.[46] Pathogenic variants often show incomplete and age-related penetrance, and variable expressivity, leading to diverse manifestations of the disease.[11] Some individuals may experience severe symptoms requiring early interventions, while others may remain unaffected or mildly affected. This variability is influenced by genetic heterogeneity, non-genetic factors like hypertension or exercise, and the co-inheritance of other genetic factors.[11] The genetic yield of DCM is estimated at 20–37 %, with over 100 related genes identified.[8,47] Advances in sequencing technologies have made it easier to discover more genes involved in DCM, reducing the cases of "idiopathic DCM".[5] Next-generation sequencing studies show that over 38 % of DCM cases have two or more variants, indicating an oligogenic inheritance pattern.[48,49] There is significant gene overlap in DCM and other cardiomyopathies or channelopathies.[50–52] The presence of multiple pathogenic variants in individuals can explain the variable penetrance and phenotypic expression seen even within the same family.[11,53]

Sarcomeric DCM represents the most frequent genetic form of DCM, involving genes encoding sarcomeric proteins: titin, myosin, actin, troponin, and tropomyosin.[54,55] TTN is the largest sarcomeric protein in the myocardium. Truncating TTN variants, leading to premature protein termination, result in abnormally truncated protein and are present in 25 % of end stage disease, 20-25 % of familial cases of DCM, and in 18 % of sporadic cases, following an autosomal dominant pattern of inheritance.[54,56] Truncation mutations in the TTN gene, which are the most common causative mutations for DCM,[36] have been linked to various conditions such as alcoholic cardiomyopathy, PPCM, and chemotherapy-related cardiomyopathy. This suggests that environmental factors may act as a second hit, alongside genetic factors, inducing DCM-like contractile dysfunction.[1] Additional variants in the ribonucleic acid binding protein (RBM20) gene, responsible for titin splicing regulation, can lead to a DCM phenotype characterized by frequent malignant VAs.[57,58]

Nuclear envelope defects, or laminopathies, are caused by mutations in the LMNA gene and account for up to 8-10 % of DCM cases.[59–61] These conditions are inherited in an autosomal dominant pattern and are characterized by an aggressive phenotype with conduction abnormalities and malignant VAs.[62] There is a high incidence of SCD, often occurring before significant LV dysfunction develops, with a 12-year mortality rate of 30 %. The median age of onset is between 30 and 40 years, with nearly complete penetrance by age 70.[63] Detecting a pathogenic LMNA variant lowers the threshold for ICD placement for primary SCD prevention, regardless of LVEF.[11]

Cytoskeletal cardiomyopathy is characterized by force transmission deficit and involves genes encoding proteins comprising the cytoskeleton like filamins, DMD, and DES.[64] Pathogenic variants in these genes are often linked to muscular dystrophies and can lead to a diverse range of cardiomyopathies.[65] DES mutations affect a muscle-specific intermediate filament, causing various cardiac and skeletal muscle issues. DMD, located on the X chromosome, plays a crucial role in linking the cytoskeleton to the extracellular matrix, with cardiac involvement common (up to 70-90 %) in Duchenne's and Becker's muscular dystrophies.[66,67] Truncation variants in FLNC are associated with severe arrhythmogenic DCM, even without apparent skeletal muscle disorders.[54] Additionally, truncating FLNC variants have been linked to both skeletal and cardiac myofibrillar myopathies, as well as a combined phenotype of left-dominant arrhythmogenic cardiomyopathy and DCM. This combined phenotype carries a heightened risk of malignant VAs and premature SCD.[68,69]

Furthermore, mutations in the BAG3 gene, which encodes an antiapoptotic protein, have been linked to the development of LV dysfunction and DCM phenotype. BAG3 gene variants are linked to DCM, exhibiting high penetrance after 40 years and posing a substantial risk of progressive HF.[70,71] Notably, a single point mutation in the BAG3 gene is associated with myofibrillar myopathies, often presenting with hypertrophic cardiomyopathy or restrictive cardiomyopathy.[72] Phenotypic variability is significant, with some mutation carriers experiencing advanced HF requiring transplantation or resulting in death, while others show no penetrance.[70] Risk factors for adverse outcomes among individuals with BAG3 pathogenic variants include male sex, decreased LVEF, and increased LVEDD.[70] Additionally, a multicenter cohort study revealed that carriers of the founder pathogenic R14del PLN variant face elevated risk of malignant VAs or end-stage HF.[73] Independent risk factors for these outcomes include sustained or non-sustained ventricular tachycardia (NSVT) and LVEF below 45 %. Notably, a poor prognosis and elevated mortality rates were observed from late adolescence

onward. Therefore, in patients diagnosed with PLN cardiomyopathy and exhibiting LVEF below 45 % or NSVT, the consideration of implanting an ICD is reasonable (class IIa).[73] In carriers of the p.S358L-TMEM43 variant, a study revealed improved survival among those treated with an ICD compared to those managed conventionally.[74] Additionally, males exhibited a poorer prognosis compared to females, with affected males experiencing hospitalization four times more frequently and a younger age at death.[75]

Genotype-phenotype studies highlight the importance of ICDs for primary prevention, even in patients without severe LV dysfunction but carrying certain genetic variants. Patients with pathogenic LMNA variants, for instance, are recognized as a high-risk group for SCD. The most recent ESC guidelines for the management of DCM emphasize the impact of phenotype on the risk of SCD. Individuals carrying disease-causing variants in genes like PLN, DSP, LMNA, FLNC, TMEM43, BAG3, and RBM20 exhibit a notably higher incidence of major arrhythmic events compared to other DCM causes, irrespective of their LVEF. Therefore, in such cases, ICD implantation for primary prevention should be considered (class IIa).[11]

Genetic testing is recommended for individuals diagnosed with DCM, with cascade screening for relatives if a pathogenic variant is found.[47] Patients with variants in arrhythmogenic genes like LMNA or FLNC may need earlier ICD implantation.[48] While genotype-negative relatives were previously considered risk-free, recent evidence suggests they have a lower, but not zero, risk.[36] These relatives may benefit from less frequent clinical screening every 2-3 years.[76] Expert interpretation of genetic results is essential, and testing should ideally be done in multidisciplinary clinics.[77] Familial screening helps identify relatives with clinical or subclinical DCM, even without a family history, aiding in early detection. First-degree relatives should undergo ECG, echocardiogram, and possibly Holter monitoring for cardiomyopathy.[78,79]

Multi-omics approaches

Studies on the functional genomic signature of DCM and ischemic cardiomyopathy (ICM) hearts have mainly focused on upstream domains, including whole-genome sequencing, transcriptomic profiling, and protein expression. These studies have highlighted key molecular changes in HF, such as extracellular matrix remodeling, inflammatory signaling, oxidative stress, mitochondrial dysfunction, and branched-chain amino acid metabolism.[80,81] However, these proteomic studies often use small sample sizes and lack matching for age, gender, and body mass index (BMI). Li M et al. showed that a key metabolite common to both ICM and DCM was thyroxine.[80] This suggests that thyroid hormones play an important role in cardiac function, as patients often have "low T3 syndrome," impacting heart health. These findings show elevated T4 in HF myocardium, supporting the idea that low cardiac T3 exacerbates HF. Flavin mononucleotide (FMN), significantly decreased in both conditions, indicates increased oxidative stress. FMN reduction has been reported in animal models, but this is the first report in human HF, highlighting its potential as a therapeutic target.[80] Both ICM and DCM showed significant changes in pyrimidine and purine nucleotides, linked to increased anaerobic glycolysis and decreased ATP production. Also, this study highlights gender-specific differences in HF, with male-specific elevations in trimethylamine N-oxide and inhibitors of nitric oxide synthase, suggesting different pathogenic pathways between sexes.[80] In another multi-omics study, the integration of transcriptomic and proteomic analyses identified 10 differentially expressed genes/proteins in DCM signature, comprising AEBP1, CA3, HBA2, HBB, HSPA2, MYH6, SERPINA3, SOD3, THBS4, and UCHL1.[81] This study emphasized extracellular matrix dysregulation and proposed potential novel diagnostic and/or therapeutic biomarkers for DCM.

DCM arises from a complex interplay of genetic and environmental factors, with intracellular phenotypes manifesting as endophenotypes at disease onset. Recent advancements in single-cell RNA sequencing have enabled molecular profiling at the cellular level, offering insights into disease mechanisms and potential treatment avenues.[82] Studies have revealed specific molecular signatures in cardiomyocytes of patients with DCM, including activation of DNA damage response and TGF-β signaling, downregulation of genes related to mitochondrial metabolism, and the presence of dopamine receptor D1 positive cardiomyocytes associated with fatal VAs.[83] Additionally, analysis before and after left ventricular assist device implantation showed restoration of mitochondrial metabolism-related gene expression.[84] Measurement of IGFBP7 from DNA damage-positive cardiomyocytes has been proposed as a marker for HF severity.[84] Further investigations have highlighted age-related changes in cardiac fibroblast proportion and gene expression profiles, as well as distinct molecular signatures associated with different clinical phenotypes of DCM, including autoimmune predisposition and arrhythmias.[84] These findings underline the potential for precise disease stratification and targeted therapies in DCM patients.

Several recent studies have utilized single-cell RNA sequencing to analyze cardiomyopathy cases and correlate them with clinical characteristics. Koenig et al. conducted single-nucleus RNA sequencing on heart nuclei from patients with DCM, revealing an increased population of monocyte-derived inflammatory cells and characteristic gene expression patterns in fibroblasts, endothelial cells, and pericytes associated with DCM.[85] Chaffin et al. performed single-nucleus RNA sequencing on hearts from patients with both DCM and HCM, identifying common fibroblast activation pathways in both conditions and assessing gene function through CRISPR-knockout screens.[86] Another study conducted single-nucleus RNA sequencing on hearts from DCM patients, observed a decrease in cardiomyocyte proportion alongside elevation in endothelial and immune cell populations.[87] While fibroblast population remained stable, they exhibited strong expression of extracellular matrix-related genes and promoted fibrosis. Notably, endothelin signaling was activated in LMNA mutant cardiomyopathy, while interleukin 6 signaling was activated in TTN mutant cardiomyopathy.[87] Additionally, a study analyzing the human fetal heart using single-cell ATAC-seq, demonstrated cell-type-specific epigenomic changes during development and illustrating how de novo mutations contribute to disease development by altering transcription factor binding and downstream gene expression.[88]

Prominent metabolites like acylcarnitines, succinic acid, malate, methylhistidine, aspartate, methionine, and phenylalanine have emerged as potential biomarkers for diagnosing DCM through metabolomics.[89] Furthermore, biomarkers such as 1-pyrroline-2-carboxylate, norvaline, lysophosphatidylinositol, phosphatidylglycerol, fatty acid esters of hydroxy fatty acid, and phosphatidylcholine play a

crucial role in distinguishing DCM from ICM.[89] Acylcarnitines, isoleucine, linoleic acid, and tryptophan are key biomarkers for tracking treatment response in DCM. Dysregulation of metabolic pathways, including branch-chain amino acid, glycolysis, tricarboxylic acid cycle, and triacylglycerol and pentose phosphate metabolism, shows promise for therapeutic interventions in this population.[89]

Sudden cardiac death prediction

Genome-wide genetic research plays a crucial role in accurately assessing disease risk. Rapid advancements in single-cell analysis are shedding light on the pathophysiology of DCM. Combining genomic analysis with single-cell molecular profiling is anticipated to enhance the detailed stratification of cardiomyopathy.[90] Moreover, utilizing machine learning techniques for multiparametric phenotyping is crucial in delineating and validating new prognostically significant subtypes of DCM and stratifying patients accordingly.[91] The predictive strength of LGE and genetic markers for VAs and SCD in DCM could greatly amplify with deeper investigations into genotype-phenotype correlations across DCM-related genes. Recent strides in long-term heart rate monitoring, high-definition CMR, and next-generation sequencing hold potential for uncovering new DCM subtypes based on genetic, metabolomics,[92] morphological, and electrophysiological profiles (Fig. 1).[93]

For years, assessing the risk of SCD in DCM patients relied on LV dysfunction severity and presence of symptoms.[8] While ICD implantation was traditionally reserved for symptomatic patients with LVEF < 35 % and a predicted survival of over a year, recent findings challenge this approach. Research increasingly supports the use of LGE in risk assessment, as it predicts mortality, hospitalization, and SCD. LGE presence, extent, and patterns offer insights into malignant VAs and LV reverse remodeling.[8] Studies suggest a stronger correlation between VAs and LGE than with LVEF, particularly in patients undergoing primary prevention ICD implantation. Due to family and sports screening, DCM patients are now often identified earlier and at asymptomatic stages. While their risk of HF-related events is low, the risk of life-threatening VAs and SCD may be elevated. Myocardial fibrosis and specific genetic substrates linked to arrhythmic phenotypes serve as additional risk stratification markers.[11] Also, the traditional approach overlooks the diversity within DCM, and emerging data indicate an elevated risk of SCD associated with specific genotypes. This shift in understanding has influenced international guidelines on ICD, advocating for lower thresholds in patients with certain genetic variants such as LMNA, FLNC, PLN, or RBM20, alongside other high-risk features beyond LVEF. These updated guidelines reflect a broader trend aiming to personalize patient care by considering both genotype and phenotype.

Genomic risk scores, derived from common genetic variations, enhance the prediction of individual susceptibility to cardiovascular conditions. While specific risk scores for DCM are yet to be developed, understanding one's genetic predisposition could impact the threshold for myocardial dysfunction in carriers of rare variants.[94] Integrating genomics risk scores for DCM-related comorbidities like AF could refine risk assessment models for DCM onset and outcomes. However, the similarity in variant prevalence between specific cardiomyopathy cohorts and idiopathic DCM suggests environmental factors might expedite disease progression rather than solely

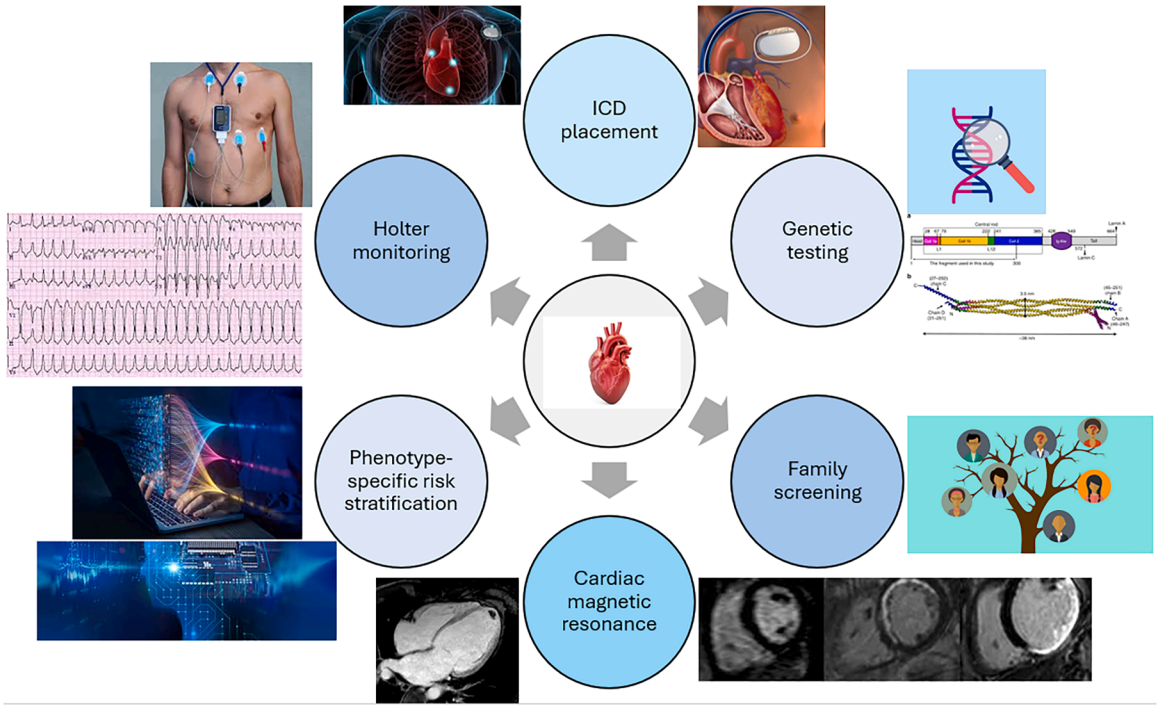

Fig. 1. Current guidelines and new insights for the prevention of SCD in patients with DCM.

triggering it.[95] Further research is imperative to clarify these gene-environment dynamics. Identifying genetic risk variants holds clinical significance, revealing why certain individuals respond less favorably to treatment or fail to improve despite stressor avoidance.[96] For instance, women carrying deleterious genetic variants in PPCM often exhibit poor recovery rates, potentially indicating familial DCM.[97] This underscores the importance of cascade testing for relatives. Prior genetic testing before planned stressors such as anthracycline chemotherapy could inform strategies to mitigate DCM risk, though feasibility and cost-effectiveness necessitate further assessment.[98] Finally, exercise oscillatory ventilation is considered one of the most powerful, independent predictors for morbidity, mortality and sudden cardiac death in patients with systolic heart failure, with a prevalence of 17-35 %.[99]

Targeted therapies and precision interventions

Current management of DCM primarily focuses on treating symptomatic patients with a "one size fits all" approach, which includes HF drug therapy (β-blockers, renin-angiotensin system inhibitors, aldosterone antagonists, sodium-glucose cotransporter-2 inhibitors, and diuretics), devices, and heart transplantation. However, this method is ineffective and unsustainable due to the persistently high morbidity and mortality rates among DCM patients.[14,36] Transitioning to individualized care and shifting the focus from treatment to prevention could improve patient outcomes and reduce healthcare costs.[8] Integration of genetic data presents novel pathways for phenotype-targeted treatment, facilitating preemptive interventions in at-risk asymptomatic individuals. Precise phenotyping for this heterogeneous disease holds paramount importance. The utilization of phenomapping, involving deep phenotyping alongside clustering analysis, has the potential to reveal patient subclasses that may benefit from tailored therapies, thereby offering invaluable guidance for treatment strategies (Table 2).[14]

Genotype directed therapy

Advancements in genetics offer promising prospects for tailoring treatments based on genotype. Understanding gene-specific mechanisms and functional effects of variants is crucial for determining appropriate therapeutic approaches. Genotype-specific medical therapies are advancing, with clinical trials investigating treatments targeting the molecular consequences of genetic causes. Selective inhibition of mitogen-activated protein kinase shows promise in laminopathies.[100] Also, gene editing therapies offer significant potential for improving outcomes in genetic diseases. Genotypes are expected to play a larger role in patient management. For many individuals with overt DCM, identifying a pathogenic variant through genetic testing may not significantly alter clinical management. However, for certain genes, knowing the precise molecular cause can influence treatment decisions.[101,102]

Targeted genetic therapy focuses on alleviating the clinical consequences associated with the mutation and targeting the molecular effects of the pathogenic variant. For instance, patients with PLN, DSP, LMNA, FLNC, TMEM43, BAG3, and RBM20 mutations often require ICD implantation at a lower threshold.[11] Moreover, severe arrhythmic DCM caused by the gain-of-function variant pR222Q in

Table 2
Targeted therapies in dilated cardiomyopathy.

Intervention	Target	Description	Clinical Evidence
Sodium-channel blockers	SCN5A R222Q variant	Sodium channels blocking	Improvement in ventricular function Arrhythmic reduction
p38 MAP kinase inhibition	LMNA mutation	Inhibits MAP kinase pathway	RCTs are needed Prevent LV dilation and dysfunction
CRISPR/Cas9 genome editing	TTN truncating mutations	Gene-editing technology to correct truncating TTN mutations	Restoring sarcomere function Experimental studies RCTs are needed
Exon skipping	TTN truncating mutations	Skips defective exons to rescue myofibril assembly	Restoring sarcomere function in cardiomyocytes
Mesenchymal progenitor cells	Anthracycline-induced DCM	Restores myocardial function damaged by anthracycline chemotherapy	SENECA trial (ongoing)
Gene correction with iPSC-derivedcardiomyocytes	TTN, PLN mutations	Corrects genetic variants in patient-specific iPSCs, then re-differentiates into functional cardiomyocytes	Reversal of DCM phenotypes in vitro in PLN R14Del mutations Restoring sarcomere structure and function
β-blockers and calcium antagonists	Various genetic mutations	Reduces the severity of the DCM phenotype by blocking β-adrenergic activity and improving calcium handling	Improved outcomes (DES, TNNT2, LMNA)
Mitogen-Activated Protein Kinase Inhibitors	LMNA mutations	Targets elevated cardiac metabolism caused by LMNA mutations	Mitigated LV dysfunction in mice Reduce LV dilation and prevent HF RCTs are needed
Pharmacogenomics	CYP2D6 polymorphisms	Determines individual drug metabolism rates, guiding personalized treatment	Genetic testing identifies poor metabolizers
ICD for primary prevention	LMNA, PLN, RBM20 variants	Early ICD placement to prevent SCD in patients with high-risk genetic variants	Strong recommendation in guidelines for patients with certain variants, regardless of LV ejection fraction

DCM, Dilated cardiomyopathy; DES, Desmoplakin; HF, Heart Failure; ICD, Implantable Cardioverter Defibrillator; iPSC, Induced Pluripotent Stem Cell; LMNA, Lamin A/C; LV, Left ventricular; MAP, Mitogen-Activated Protein; PLN; phospholamban; RBM20, RNA Binding Motif Protein 20; RCTs, Randomized Controlled Trials; SCD, sudden cardiac death; SCN5A, Sodium Voltage-Gated Channel Alpha Subunit 5; TTN, Titin.

the SCN5A gene responds dramatically to sodium-channel blocking drugs, showing significant improvement in ventricular function and reduction in arrhythmic burden, unlike standard HF therapies.[103] This emphasizes the significance of functional genomics in identifying treatable variants. Additionally, increased cardiac activity of ERK1/2, JNK, and p38 MAP kinases has been observed in LMNA-mutated mice. Inhibition of p38 effectively mitigated LV dilation and dysfunction, leading to the initiation of a phase III clinical trial (NCT03439514) targeting symptomatic DCM patients with the LMNA variant. However, this trial was discontinued due to its unlikely ability to meet its primary endpoint.[100] Truncating mutations in the TTN gene elevate cardiac metabolism, leading to sarcomere dysfunction and DCM progression. Targeting these metabolic alterations offers a potential gene-directed treatment.[104]

The ultimate therapy is to target genetic disruption specific to each individual patient. Various methods are being evaluated for their potential efficacy in treating DCM, including CRISPR/Cas9 technology, exon skipping, and gene replacement therapy.[105] Nucleases like CRISPR/Cas are efficient for targeted editing, but delivery via adeno-associated virus (AAV) vectors still carries risks.[6] Despite challenges, CRISPR/Cas9 remains the leading tool for precise genome editing.[106] Various gene-editing methods hold promise for directly altering variants such as DMD mutations, as demonstrated in dystrophic mice.[107] In the CRISPR/Cas9 system, RNA sequences target genes for Cas9 enzyme cutting, leading to double-strand breaks repairable via non-homologous end joining (NHEJ) or homology-directed repair (HDR).[6] NHEJ often causes indels, knocking out the target gene, while HDR enables specific changes like knock-in mutations.[108] Recent adaptations include base editing, converting base pairs without breaks, and prime editing, which makes precise edits without breaks using reverse transcriptase. Both techniques have demonstrated efficacy in introducing mutations and insertions.[108] Dave et al. evaluated CRISPR/Cas9-mediated genome editing's therapeutic effects in mice with PLN9 gene mutations using cardiotropic AAV9 vectors.[109] They found that gene editing reduced ventricular dilation, stroke volume, and susceptibility to ventricular tachycardia. Similarly, Hakim et al. showed that increasing gRNA vector doses enhanced DMD expression in mice with DMD gene mutations, indicating potential for DMD specific treatment.[110] El Refaey et al. demonstrated the feasibility of systemic AAV rh.74-mediated CRISPR/Cas9 delivery for genome editing in mdx mice.[107] However, delivery of CRISPR-Cas9 to human cardiomyocytes presents a significant challenge despite success in animal studies, primarily due to reliance on viral vectors, which can provoke immune reactions and other adverse effects. Off-target effects are another concern, as CRISPR-Cas9 may inadvertently target non-intended genomic regions, particularly problematic in the complex genetic landscape of DCM.[108] Moreover, CRISPR-Cas9′s efficacy is limited to certain genomic regions, such as exons, while DCM-causing mutations may occur elsewhere. Additionally, DCM often involves mutations in multiple genes, necessitating multi-pronged treatment approaches. Exon skipping, especially effective for truncating mutations, involves removing the exon with new stop-codon, preventing incomplete transcripts.[111] Notably, in TTN truncating mutations, which are the most common in DCM, this approach could rescue defective myofibril assembly and stability in patient-specific cardiomyocytes derived from induced pluripotent stem cells (iPSCs).[112]

An increasingly appealing method involves utilizing iPSCs and differentiating them into cardiomyocytes (iPSCs-CMs). Research utilizing iPSC—CM modeling has investigated various genetic variants including LMNA, DES, TNNT2, PLN, RBM20, and TTN.[113–118] These studies commonly report sarcomere disruption, reduced contractile force, and impaired calcium regulation. In vivo experiments with β-blockers and calcium antagonists have shown a reduction in phenotype severity. Notably, two iPSC—CM studies targeting PLN R14Del achieved complete phenotype reversal in vitro through targeted gene correction.[119] These studies highlight the potential of iPSC-based disease models and high-throughput screening approaches to identify novel therapeutic targets for genetic DCM. However, the use of iPSC—CMs is limited by their relative immaturity, the monoculture of a single cardiac cell type, inherent technical and biological variability, and the lack of an appropriate neurohumoral and contractile environment.[113] Generating 3-dimensional cardiac organoids from cocultured iPSC—CMs, fibroblasts, endothelial cells, and other cell types is feasible, enabling a more accurate simulation of heart muscle structure and function. However, these engineered heart tissues pose challenges such as complexity, limited scalability, and difficulties in achieving consistent cell composition and maturity, electrical coupling, as well as oxygen and nutrient supply.[120]

Cardiotoxicity-directed therapy

Toxic agents causing direct damage to the myocardium are well-recognized etiologies of DCM. Anthracyclines, for instance, exhibit cardiotoxic effects through various pathogenic pathways, such as heightened oxidative stress, modulation of topoisomerase activity, changes in multidrug-resistant efflux proteins, and reduction in mesenchymal progenitor cells.[121] The decline in mesenchymal progenitor cells diminishes the heart's regenerative ability when subjected to stress. The SENECA trial, aA randomized, placebo-controlled trial study is currently assessing the safety and feasibility of administering mesenchymal progenitor cells to patients with anthracycline-induced DCM (NCT02509156).[122] The SENECA trial aims to establish a targeted treatment approach for chemotherapy-induced DCM, complementing prompt administration of general HF therapy.

Anti-inflammatory and antiviral therapy

A prospective randomized controlled trial (RCT) involving 102 patients with idiopathic DCM showed that prednisone administration led to a statistically significant, albeit modest, improvement in LVEF after 3 months.[123] Another three RCTs assessed the efficacy of immunosuppression in DCM patients, but without molecular analysis for viral infection, they showed no beneficial effect on mortality or cardiac function.[124–126] The TIMIC trial conducted by Frustaci et al. was the sole study to demonstrate favorable outcomes with an immunosuppressive regimen in patients with inflammatory DCM.[125] However, its limited sample size of only 85 patients, absence of a median follow-up exceeding one year, and lack of a control population leave the clinical implications uncertain. Also, the role of anti-interleukin 1 has been evaluated with some small pilot studies showing promising results.[127,128] However, its effectiveness

needs to be validated with larger randomized trials. Moreover, in a prospective case-control study involving 34 idiopathic IDC patients, immunoadsorption significantly improved cardiac function and clinical status by eliminating autoantibodies against β1-adrenoceptors (β1-AABs), suggesting it may be an effective treatment to delay or avoid heart transplantation.[124] Another prospective study involving 22 DCM patients demonstrated that immunoadsorption therapy provides significant hemodynamic improvements in patients with DCM, but these benefits are not directly linked to the removal of β1-adrenergic receptor autoantibodies, suggesting other mechanisms are involved.[129] Also, a double-blind, randomized study by Gullestad L et al. involving 40 patients with chronic congestive HF found that intravenous immunoglobulin (IVIG) significantly increased anti-inflammatory cytokines and improved LVEF compared to placebo.[130] The study suggests that IVIG therapy may offer additional benefits in modulating inflammation and improving cardiac function in CHF patients alongside conventional treatments. A multicenter, randomized, double-blind trial investigated the effects of immunoadsorption (IA) with subsequent immunoglobulin G (IgG) substitution in patients with DCM, revealing that the removal of cardiac autoantibodies, particularly IgG-3 subclass antibodies, led to significant improvements in cardiac function, including LVEF, cardiac index, and stroke volume index, suggesting IA as a potential therapeutic strategy for DCM patients with HF.[131] Viral agents like herpes simplex, cytomegalovirus, Epstein-Barr, parvovirus, hepatitis C, or human immunodeficiency virus have been identified in DCM patients. However, trials using specific antiviral agents or intravenous immunoglobulins failed to demonstrate any treatment benefit in these cases.[132]

Stem cell therapy

A systematic review of 13 RCTs comparing stem/progenitor cells with no cells in adults with non-ischaemic DCM demonstrated that there is no clear evidence that stem cell therapy (SCT) provides significant benefits in reducing all-cause mortality, improving health-related quality of life, or enhancing exercise capacity in people with DCM.[133] SCT may offer slight improvements in functional class and certain physiological measures, but these effects are uncertain due to the low quality of the evidence.[133] Further research, including ongoing studies, is needed to establish the role of SCT in treating DCM and to determine the most effective treatment modalities. For now, SCT should remain within clinical research settings.[133] Also, the "Stem Cell Therapy in Non-Ischemic Non--treatable Dilated Cardiomyopathies II" trial (NCT03797092) is an ongoing pilot study testing the safety and efficacy of allogeneic adipose-derived stromal cells in improving myocardial function in patients with non-ischemic DCM and HF, with primary results focused on changes in LV function.[134]

Pharmacogenomics

The determination of genetic contribution to individual variation in pharmacotherapy responses is important in cardiovascular diseases. While clinical characteristics such as age, sex, ethnicity, and BMI play a significant role in determining the optimal drug and dosage for each patient, they may not suffice, as genetic polymorphisms in drug-metabolizing enzymes also often contribute to variability. For instance, the hepatic elimination of β-blockers, a commonly used drug in clinical practice and HF management, relies heavily on CYP2D6.[135] This enzyme exhibits high polymorphism, with varying prevalence of genetic variations across ethnicities. Metoprolol, one of the most utilized β-blockers, undergoes 70-80 % of its metabolism through this pathway.[135] Clinical studies have demonstrated that poor metabolizers of CYP2D6 exhibit 3 to 10 times higher plasma concentrations of metoprolol compared to extensive metabolizers with normal CYP2D6 activity.[136,137] Additionally, genetic variations in the β1-adrenergic receptor gene may account for interindividual differences in response to β-blockers.[135] Genetic polymorphisms in the adrenergic signaling pathway serve as significant risk factors or modifiers of cardiovascular disease.[138]

Conclusion

DCM is a complex and heterogeneous disease characterized by various etiologies and phenotypes, all leading to advanced HF. Enhanced comprehension of the DCM phenotypes, coupled with recent advances in multi-omics and high-throughput technologies for delineating the DCM genome, proteome, and metabolome, promises to refine diagnostic, preventive, prognostic, and therapeutic strategies for this condition. By unraveling the complex pathogenic mechanisms of DCM and closely aligning with the disease phenotype, precision medicine presents an opportunity to shape both preventive measures and therapeutic interventions. Additionally, novel methods for risk stratification and prognostication, such as machine learning, improve the accuracy of predicting disease progression and outcomes. It is crucial to link key disease-driving mechanisms in DCM patients with targeted therapies. As the genetic components of DCM become increasingly understood, we are entering a period of rapid translation to precision medicine-based treatments. Therapies targeting underlying causes, such as gene therapies and primary disease pathway modulators, as well as pharmacogenomics, hold the potential to substantially alleviate disease burden and improve patient outcomes.

CRediT authorship contribution statement

Elina Khattab: Writing – original draft. **Michael M Myrianthefs:** Writing – original draft. **Stefanos Sakellaropoulos:** Writing – original draft. **Kyriakos Alexandrou:** Writing – original draft. **Andreas Mitsis:** Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

References

1. Nomura S, Ono M. Precision and genomic medicine for dilated and hypertrophic cardiomyopathy. *Front Cardiovasc Med*. 2023;10, 1137498. https://doi.org/10.3389/fcvm.2023.1137498. Mar 6PMID: 36950287; PMCID: PMC10025380.
2. Kinnamon DD, Morales A, Bowen DJ, Burke W, Hershberger RE, DCM Consortium*. Toward genetics-driven early intervention in dilated cardiomyopathy: design and implementation of the DCM precision medicine study. *Circ Cardiovasc Genet*. 2017;10(6), e001826. https://doi.org/10.1161/CIRCGENETICS.117.001826. PMID: 29237686, PMCID: PMC5842914.
3. Harding D, Chong MHA, Lahoti N, et al. Dilated cardiomyopathy and chronic cardiac inflammation: pathogenesis, diagnosis and therapy. *J Intern Med*. 2023;293(1):23–47. https://doi.org/10.1111/joim.13556. PMID: 36030368.
4. Charron P, Elliott PM, Gimeno JR, et al. The cardiomyopathy registry of the EURObservational research programme of the European society of cardiology: baseline data and contemporary management of adult patients with cardiomyopathies. *Eur Heart J*. 2018;39(20):1784–1793. https://doi.org/10.1093/eurheartj/ehx819. PMID: 29378019.
5. Eldemire R, Mestroni L, Taylor MRG. Genetics of dilated cardiomyopathy. *Annu Rev Med*. 2024;75:417–426. https://doi.org/10.1146/annurev-med-052422-020535. PMID: 37788487, PMCID: PMC10842880.
6. Helms AS, Thompson AD, Day SM. Translation of new and emerging therapies for genetic cardiomyopathies. *JACC Basic Transl Sci*. 2021;7(1):70–83. https://doi.org/10.1016/j.jacbts.2021.07.012. Published 2021 Dec 1PMID: 35128211, PMCID: PMC8807730.
7. Reichart D, Magnussen C, Zeller T, Blankenberg S. Dilated cardiomyopathy: from epidemiologic to genetic phenotypes: a translational review of current literature. *J Intern Med*. 2019;286(4):362–372. https://doi.org/10.1111/joim.12944. PMID: 31132311.
8. Javed S, Halliday BP. Precision therapy in dilated cardiomyopathy: pipedream or paradigm shift? *Camb Prism Precis Med*. 2023;1:e34. https://doi.org/10.1017/pcm.2023.24. Published 2023 Nov 20. PMID: 38550947, PMCID: PMC10953759.
9. McNally EM, Mestroni L. Dilated cardiomyopathy: genetic determinants and mechanisms. *Circ Res*. 2017;121(7):731–748. https://doi.org/10.1161/CIRCRESAHA.116.309396. PMID: 28912180, PMCID: PMC5626020.
10. Caforio AL, Mahon NG, Baig MK, et al. Prospective familial assessment in dilated cardiomyopathy: cardiac autoantibodies predict disease development in asymptomatic relatives. *Circulation*. 2007;115(1):76–83. https://doi.org/10.1161/CIRCULATIONAHA.106.641472. PMID: 17179019.
11. Arbelo E, Protonotarios A, Gimeno JR, et al. 2023 ESC guidelines for the management of cardiomyopathies. *Eur Heart J*. 2023;44(37):3503–3626. https://doi.org/10.1093/eurheartj/ehad194.
12. Moeinafshar A, Yazdanpanah N, Rezaei N. Diagnostic biomarkers of dilated cardiomyopathy. *Immunobiology*. 2021;226(6), 152153. https://doi.org/10.1016/j.imbio.2021.152153. PMID: 37622657.
13. Sinagra G, Elliott PM, Merlo M. Dilated cardiomyopathy: so many cardiomyopathies!. *Eur Heart J*. 2020;41(39):3784–3786. https://doi.org/10.1093/eurheartj/ehz908. PMID: 31872205.
14. Verdonschot JAJ, Hazebroek MR, Ware JS, Prasad SK, Heymans SRB. Role of targeted therapy in dilated cardiomyopathy: the challenging road toward a personalized approach. *J Am Heart Assoc*. 2019;8(11), e012514. https://doi.org/10.1161/JAHA.119.012514. PMID: 31433726, PMCID: PMC6585365.
15. Peters S, Johnson R, Birch S, Zentner D, Hershberger RE, Fatkin D. Familial dilated cardiomyopathy. *Heart Lung Circ*. 2020;29(4):566–574. https://doi.org/10.1016/j.hlc.2019.11.018. PMID: 31974027.
16. Cho KW, Lee J, Kim Y. Genetic variations leading to familial dilated cardiomyopathy. *Mol Cells*. 2016;39(10):722–727. https://doi.org/10.14348/molcells.2016.0061. PMID: 27802374, PMCID: PMC5104879.
17. Jain A, Norton N, Bruno KA, Cooper Jr LT, Atwal PS, Fairweather D. Sex differences, genetic and environmental influences on dilated cardiomyopathy. *J Clin Med*. 2021;10(11):2289. https://doi.org/10.3390/jcm10112289. Published 2021 May 25. PMID: 34070351, PMCID: PMC8197492.
18. Day E, Rudd JHF. Alcohol use disorders and the heart. *Addiction*. 2019;114(9):1670–1678. https://doi.org/10.1111/add.14703. PMID: 31309639, PMCID: PMC6771559.
19. Arenas DJ, Beltran S, Zhou S, Goldberg LR. Cocaine, cardiomyopathy, and heart failure: a systematic review and meta-analysis. *Sci Rep*. 2020;10(1), 19795. https://doi.org/10.1038/s41598-020-76273-1. Published 2020 Nov 13PMID: 33188223, PMCID: PMC7666138.
20. Tschöpe C, Ammirati E, Bozkurt B, et al. Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. *Nat Rev Cardiol*. 2021;18(3):169–193. https://doi.org/10.1038/s41569-020-00435-x. PMID: 33046850, PMCID: PMC7548534.
21. da Cunha S, Albanesi Filho FM, da Cunha Bastos VL, Antelo DS, Souza MM. Thiamin, selenium, and copper levels in patients with idiopathic dilated cardiomyopathy taking diuretics. *Arq Bras Cardiol*. 2002;79(5):454–465. https://doi.org/10.1590/s0066-782x2002001400003. PMID: 12447496.
22. Marinescu V, McCullough PA. Nutritional and micronutrient determinants of idiopathic dilated cardiomyopathy: diagnostic and therapeutic implications. *Expert Rev Cardiovasc Ther*. 2011;9(9):1161–1170. https://doi.org/10.1586/erc.11.95. PMID: 21932959.
23. Kang N, Friedrich MG, Abramov D, Martinez-Naharro A, Fontana M, Parwani P. Viral myocarditis and dilated cardiomyopathy as a consequence-changing insights from advanced imaging. *Heart Fail Clin*. 2023;19(4):445–459. https://doi.org/10.1016/j.hfc.2023.03.009. PMID: 37714586.
24. Davis MB, Arany Z, McNamara DM, Goland S, Elkayam U. Peripartum cardiomyopathy: JACC state-of-the-art review. *J Am Coll Cardiol*. 2020;75(2):207–221. https://doi.org/10.1016/j.jacc.2019.11.014.
25. Patel AR, Kramer CM. Role of cardiac magnetic resonance in the diagnosis and prognosis of nonischemic cardiomyopathy. *JACC Cardiovasc Imaging*. 2017;10:1180–1193. https://doi.org/10.1016/j.jcmg.2017.08.005, 10 Pt APMID: 28982571, PMCID: PMC5708889.
26. Chevalier C, Kremer K, Cavus E, et al. CMR feature tracking in patients with dilated cardiomyopathy: patterns of myocardial strain and focal fibrosis. *Open Heart*. 2022;9(2), e002013. https://doi.org/10.1136/openhrt-2022-002013. PMID: 36522125, PMCID: PMC9756283.
27. Maisch B, Pankuweit S. Inflammatory dilated cardiomyopathy: etiology and clinical management. Inflammatorische dilatative kardiomyopathie: ätiologie und klinisches management. *Herz*. 2020;45(3):221–229. https://doi.org/10.1007/s00059-020-04900-8. PMID: 32123933, PMCID: PMC7198648.
28. Merlo M, Zaffalon D, Stolfo D, et al. ECG in dilated cardiomyopathy: specific findings and long-term prognostic significance. *J Cardiovasc Med (Hagerstown)*. 2019;20(7):450–458. https://doi.org/10.2459/JCM.0000000000000804. PMID: 30985353.
29. Finocchiaro G, Papadakis M, Dhutia H, et al. Electrocardiographic differentiation between 'benign T-wave inversion' and arrhythmogenic right ventricular cardiomyopathy. *Europace*. 2019;21(2):332–338. https://doi.org/10.1093/europace/euy179. PMID: 30169617.
30. Grimm W, Christ M, Bach J, Müller HH, Maisch B. Noninvasive arrhythmia risk stratification in idiopathic dilated cardiomyopathy: results of the Marburg cardiomyopathy study. *Circulation*. 2003;108(23):2883–2891. https://doi.org/10.1161/01.CIR.0000100721.52503.85. PMID: 14623812.
31. Puggia I, Merlo M, Barbati G, et al. Natural history of dilated cardiomyopathy in children. *J Am Heart Assoc*. 2016;5(7), e003450. https://doi.org/10.1161/JAHA.116.003450. Published 2016 Jun 30. PMID: 27364989, PMCID: PMC5015381.
32. Rossi A, Dini FL, Faggiano P, et al. Independent prognostic value of functional mitral regurgitation in patients with heart failure. A quantitative analysis of 1256 patients with ischaemic and non-ischaemic dilated cardiomyopathy. *Heart*. 2011;97(20):1675–1680. https://doi.org/10.1136/hrt.2011.225789. PMID: 21807656.
33. Losurdo P, Stolfo D, Merlo M, et al. Early arrhythmic events in idiopathic dilated cardiomyopathy. *JACC Clin Electrophysiol*. 2016;2(5):535–543. https://doi.org/10.1016/j.jacep.2016.05.002. PMID: 29759572, PMCID: PMC9689767.

34. Puwanant S, Priester TC, Mookadam F, Bruce CJ, Redfield MM, Chandrasekaran K. Right ventricular function in patients with preserved and reduced ejection fraction heart failure. *Eur J Echocardiogr*. 2009;10(6):733–737. https://doi.org/10.1093/ejechocard/jep052. PMID: 19443468.
35. Pinamonti B, Di Lenarda A, Sinagra G, Camerini F. Restrictive left ventricular filling pattern in dilated cardiomyopathy assessed by doppler echocardiography: clinical, echocardiographic and hemodynamic correlations and prognostic implications. Heart Muscle Disease Study Group. *J Am Coll Cardiol*. 1993;22(3): 808–815. https://doi.org/10.1016/0735-1097(93)90195-7. PMID: 8354816.
36. Fatkin D, Huttner IG, Kovacic JC, Seidman JG, Seidman CE. Precision medicine in the management of dilated cardiomyopathy: JACC state-of-the-art review. *J Am Coll Cardiol*. 2019;74(23):2921–2938. https://doi.org/10.1016/j.jacc.2019.10.011. PMID: 31806137.
37. Sepehrkhouy S, Gho JMIH, van Es R, et al. Distinct fibrosis pattern in desmosomal and phospholamban mutation carriers in hereditary cardiomyopathies. *Heart Rhythm*. 2017;14(7):1024–1032. https://doi.org/10.1016/j.hrthm.2017.03.034. PMID: 28365402.
38. Zhang T, Xue Q, Zhu R, Jiang Y. Diagnostic value of PICP and PIIINP in myocardial fibrosis: a systematic review and meta-analysis. *Clin Cardiol*. 2022;5. https://doi.org/10.1002/clc.23901. Published online DecemberPMID: 36468277.
39. Lazar-Poloczek E, Romuk E, Jacheć W, Wróbel-Nowicka K, Świętek A, Wojciechowska C. Association of NT-proBNP and sST2 with left ventricular ejection fraction and oxidative stress in patients with stable dilated cardiomyopathy. *Biomedicines*. 2024;12(4):707. https://doi.org/10.3390/biomedicines12040707. Published 2024 Mar 22PMID: 38672063, PMCID: PMC11048168.
40. Li X, Chen C, Gan F, Wang Y, Ding L, Hua W. Plasma NT pro-BNP, hs-CRP and big-ET levels at admission as prognostic markers of survival in hospitalized patients with dilated cardiomyopathy: a single-center cohort study. *BMC Cardiovasc Disord*. 2014;14:67. https://doi.org/10.1186/1471-2261-14-67. Published 2014 May 11PMID: 24885051, PMCID: PMC4041639.
41. Kayvanpour E, Sedaghat-Hamedani F, Li DT, et al. Prognostic value of circulating fibrosis biomarkers in dilated cardiomyopathy (DCM): insights into clinical outcomes. *Biomolecules*. 2024;14(9):1137. https://doi.org/10.3390/biom14091137. Published 2024 Sep 9. PMID: 39334904, PMCID: PMC11430616.
42. Sakellaropoulos S, Lekaditi D, Svab S. Cardiopulmonary exercise test in heart failure: a sine qua non. *International Journal of Physical Education, Fitness and Sports*. 2020;9(2):01–08.
43. Sakellaropoulos S, Mitsis A. Cardiopulmonary exercise test-the revolving door of left ventricular assist devices in heart failure. *Curr Probl Cardiol*. 2021;46(3), 100651. https://doi.org/10.1016/j.cpcardiol.2020.100651. Mar10.1016/j.cpcardiol.2020.100651. Epub 2020 Jul 22. PMID: 32829935.
44. Tayal U, Prasad S, Cook SA. Genetics and genomics of dilated cardiomyopathy and systolic heart failure. *Genome Med*. 2017;9(1):20. https://doi.org/10.1186/s13073-017-0410-8. Published 2017 Feb 22. PMID: 28228157, PMCID: PMC5322656.
45. Garcia-Pavia P, Cobo-Marcos M, Guzzo-Merello G, et al. Genetics in dilated cardiomyopathy. *Biomark Med*. 2013;7(4):517–533. https://doi.org/10.2217/bmm.13.77. PMID: 23905888.
46. Paldino A, Dal Ferro M, Stolfo D, et al. Prognostic prediction of genotype vs phenotype in genetic cardiomyopathies. *J Am Coll Cardiol*. 2022;80(21):1981–1994. https://doi.org/10.1016/j.jacc.2022.08.804.
47. Favalli V, Serio A, Grasso M, Arbustini E. Genetic causes of dilated cardiomyopathy. *Heart*. 2016;102(24):2004–2014. https://doi.org/10.1136/heartjnl-2015-308190. PMID: 27634407.
48. Morales A, Kinnamon DD, Jordan E, et al. DCM precision medicine study of the DCM consortium; DCM consortium institutions and personnel participating in this study: study principal investigator and co-investigators, DCM consortium clinical site principal investigators and clinical site other significant contributors (OSC). The following clinical sites and individuals contributed to the submission of RO 1 H L 128857 as Site Principal Investigators (Site Pl) or as other Significant contributors (OSC),Dr. Huggins also served as study co-principal investigator,the following clinical site was added following approval of NHGRI supplemental funding but prior to initiation of enrollment,the following clinical sites were added following study activation. Variant interpretation for dilated cardiomyopathy: refinement of the American College of Medical Genetics and Genomics/ClinGen Guidelines for the DCM Precision Medicine Study. *Circ Genom Precis Med*. 2020;13(2), e002480. https://doi.org/10.1161/CIRCGEN.119.002480. AprPMID: 32160020; PMCID: PMC8070981Epub 2020 Mar 11.
49. Yeh JK, Liu WH, Wang CY, et al. Targeted next generation sequencing for genetic mutations of dilated cardiomyopathy. *Acta Cardiol Sin*. 2019;35(6):571–584. https://doi.org/10.6515/ACS.201911_35(6).20190402A. PMID: 31879508, PMCID: PMC6859096.
50. Hershberger RE, Givertz MM, Ho CY, et al. Genetic evaluation of cardiomyopathy: a clinical practice resource of the American college of medical genetics and genomics (ACMG). *Genet Med*. 2018;20(9):899–909. https://doi.org/10.1038/s41436-019-0521-2. PMID: 2990416010.1038/s41436-018-0039-z.
51. Walsh R, Offerhaus JA, Tadros R, Bezzina CR. Minor hypertrophic cardiomyopathy genes, major insights into the genetics of cardiomyopathies. *Nat Rev Cardiol*. 2022;19(3):151–167. https://doi.org/10.1038/s41569-021-00608-2. PMID: 34526680.
52. Pugh TJ, Kelly MA, Gowrisankar S, et al. The landscape of genetic variation in dilated cardiomyopathy as surveyed by clinical DNA sequencing. *Genet Med*. 2014;16(8):601–608. https://doi.org/10.1038/gim.2013.204. PMID: 24503780.
53. McGurk KA, Zhang X, Theotokis P, et al. The penetrance of rare variants in cardiomyopathy-associated genes: a cross-sectional approach to estimating penetrance for secondary findings. *Am J Hum Genet*. 2023;110(9):1482–1495. https://doi.org/10.1016/j.ajhg.2023.08.003. PMID: 37652022, PMCID: PMC10502871.
54. Herman DS, Lam L, Taylor MR, et al. Truncations of titin causing dilated cardiomyopathy. *N Engl J Med*. 2012;366(7):619–628. https://doi.org/10.1056/NEJMoa1110186. PMID: 22335739, PMCID: PMC3660031.
55. Roberts AM, Ware JS, Herman DS, et al. Integrated allelic, transcriptional, and phenomic dissection of the cardiac effects of titin truncations in health and disease. *Sci Transl Med*. 2015;7(270). https://doi.org/10.1126/scitranslmed.3010134, 270ra6PMID: 25589632, PMCID: PMC4560092.
56. Norton N, Li D, Rampersaud E, et al. Exome sequencing and genome-wide linkage analysis in 17 families illustrate the complex contribution of TTN truncating variants to dilated cardiomyopathy. *Circ Cardiovasc Genet*. 2013;6(2):144–153. https://doi.org/10.1161/CIRCGENETICS.111.000062. PMID: 23418287, PMCID: PMC3815606.
57. Filonenko K, Katus HA, Meder B. Precision medicine approach to genetic cardiomyopathy. Herangehensweise an genetische kardiomyopathie mithilfe der "precision medicine". *Herz*. 2017;42(5):468–475. https://doi.org/10.1007/s00059-017-4592-z. PMID: 28653114.
58. Nishiyama T, Zhang Y, Cui M, et al. Precise genomic editing of pathogenic mutations in RBM20 rescues dilated cardiomyopathy. *Sci Transl Med*. 2022;14(672). https://doi.org/10.1126/scitranslmed.ade1633. eade1633. PMID: 36417486, PMCID: PMC10088465.
59. Tobita T, Nomura S, Fujita T, et al. Genetic basis of cardiomyopathy and the genotypes involved in prognosis and left ventricular reverse remodeling. *Sci Rep*. 2018;8(1). https://doi.org/10.1038/s41598-018-20114-9, 1998. Published 2018 Jan 31. PMID: 29386531, PMCID: PMC5792481.
60. Jordan E, Peterson L, Ai T, et al. Evidence-based assessment of genes in dilated cardiomyopathy. *Circulation*. 2021;144(1):7–19. https://doi.org/10.1161/CIRCULATIONAHA.120.053033. PMID: 33947203, PMCID: PMC8247549.
61. In Hershberger RE, Jordan E, et al. LMNA-related dilated cardiomyopathy. eds. In: Adam MP, Feldman J, Mirzaa GM, et al., eds. *GeneReviews®*. Seattle (WA): University of Washington, Seattle; 2008. June 12.
62. Hasselberg NE, Haland TF, Saberniak J, et al. Lamin A/C cardiomyopathy: young onset, high penetrance, and frequent need for heart transplantation. *Eur Heart J*. 2018;39(10):853–860. https://doi.org/10.1093/eurheartj/ehx596. PMID: 29095976, PMCID: PMC5939624.
63. van Rijsingen IA, Arbustini E, Elliott PM, et al. Risk factors for malignant ventricular arrhythmias in lamin a/c mutation carriers a European cohort study. *J Am Coll Cardiol*. 2012;59(5):493–500. https://doi.org/10.1016/j.jacc.2011.08.078. PMID: 22281253.
64. Brandão M, Bariani R, Rigato I, Bauce B. Desmoplakin cardiomyopathy: comprehensive review of an increasingly recognized entity. *J Clin Med*. 2023;12(7): 2660. https://doi.org/10.3390/jcm12072660. Published 2023 Apr 3. PMID: 37048743, PMCID: PMC10095332.
65. Hershberger RE, Hedges DJ, Morales A. Dilated cardiomyopathy: the complexity of a diverse genetic architecture. *Nat Rev Cardiol*. 2013;10(9):531–547. https://doi.org/10.1038/nrcardio.2013.105. PMID: 23900355.
66. D'Amario D, Gowran A, Canonico F, et al. Dystrophin cardiomyopathies: clinical management, molecular pathogenesis and evolution towards precision medicine. *J Clin Med*. 2018;7(9):291. https://doi.org/10.3390/jcm7090291. Published 2018 Sep 19. PMID: 30235804, PMCID: PMC6162458.
67. Johnson R, Otway R, Chin E, et al. DMD-associated dilated cardiomyopathy: genotypes, phenotypes, and phenocopies. *Circ Genom Precis Med*. 2023;16(5): 421–430. https://doi.org/10.1161/CIRCGEN.123.004221. PMID: 37671549, PMCID: PMC10592075.

68. Vorgerd M, van der Ven PF, Bruchertseifer V, et al. A mutation in the dimerization domain of filamin c causes a novel type of autosomal dominant myofibrillar myopathy. *Am J Hum Genet*. 2005;77(2):297–304. https://doi.org/10.1086/431959. PMID: 15929027, PMCID: PMC1224531.
69. Ortiz-Genga MF, Cuenca S, Dal Ferro M, et al. Truncating FLNC mutations are associated with high-risk dilated and arrhythmogenic cardiomyopathies. *J Am Coll Cardiol*. 2016;68(22):2440–2451. https://doi.org/10.1016/j.jacc.2016.09.927. PMID: 27908349.
70. Norton N, Li D, Rieder MJ, et al. Genome-wide studies of copy number variation and exome sequencing identify rare variants in BAG3 as a cause of dilated cardiomyopathy. *Am J Hum Genet*. 2011;88(3):273–282. https://doi.org/10.1016/j.ajhg.2011.01.016. PMID: 21353195, PMCID: PMC3059419.
71. Selcen D, Muntoni F, Burton BK, et al. Mutation in BAG3 causes severe dominant childhood muscular dystrophy. *Ann Neurol*. 2009;65(1):83–89. https://doi.org/10.1002/ana.21553. PMID: 19085932, PMCID: PMC2639628.
72. Domínguez F, Cuenca S, Bilińska Z, et al. Dilated cardiomyopathy due to BLC2-associated athanogene 3 (BAG3) mutations. *J Am Coll Cardiol*. 2018;72(20):2471–2481. https://doi.org/10.1016/j.jacc.2018.08.2181. PMID: 30442290, PMCID: PMC6688826.
73. van Rijsingen IA, van der Zwaag PA, Groeneweg JA, et al. Outcome in phospholamban R14del carriers: results of a large multicentre cohort study. *Circ Cardiovasc Genet*. 2014;7(4):455–465. https://doi.org/10.1161/CIRCGENETICS.113.000374. PMID: 24909667.
74. Hodgkinson KA, Connors SP, Merner N, et al. The natural history of a genetic subtype of arrhythmogenic right ventricular cardiomyopathy caused by a p.S358L mutation in TMEM43. *Clin Genet*. 2013;83(4):321–331. https://doi.org/10.1111/j.1399-0004.2012.01919.x. PMID: 22725725.
75. Merner ND, Hodgkinson KA, Haywood AF, et al. Arrhythmogenic right ventricular cardiomyopathy type 5 is a fully penetrant, lethal arrhythmic disorder caused by a missense mutation in the TMEM43 gene. *Am J Hum Genet*. 2008;82(4):809–821. https://doi.org/10.1016/j.ajhg.2008.01.010. PMID: 18313022, PMCID: PMC2427209.
76. Mason S, Quinn E, Halliday BP. The promise and challenges of precision medicine in dilated cardiomyopathy. *Eur Heart J Case Rep*. 2021;5(11). https://doi.org/10.1093/ehjcr/ytab391. ytab391. Published 2021 Oct 1. PMID: 34746638, PMCID: PMC8567069.
77. van de Vegte YJ, Eppinga RN, van der Ende MY, et al. Genetic insights into resting heart rate and its role in cardiovascular disease. *Nat Commun*. 2023;14(1):4646. https://doi.org/10.1038/s41467-023-39521-2. Published 2023 Aug 2PMID: 37532724, PMCID: PMC10397318.
78. Vissing CR, Espersen K, Mills HL, et al. Family screening in dilated cardiomyopathy: prevalence, incidence, and potential for limiting follow-up. *JACC Heart Fail*. 2022;10(11):792–803. https://doi.org/10.1016/j.jchf.2022.07.009. PMID: 36328645.
79. Ni H, Jordan E, Kinnamon DD, et al. Screening for dilated cardiomyopathy in at-risk first-degree relatives. *J Am Coll Cardiol*. 2023;81(21):2059–2071. https://doi.org/10.1016/j.jacc.2023.03.419. PMID: 37225358, PMCID: PMC10563038.
80. Li M, Parker BL, Pearson E, et al. Core functional nodes and sex-specific pathways in human ischaemic and dilated cardiomyopathy. *Nat Commun*. 2020;11(1):2843. https://doi.org/10.1038/s41467-020-16584-z. Published 2020 Jun 2PMID: 32487995, PMCID: PMC7266817.
81. Portokallidou K, Dovrolis N, Ragia G, Atzemian N, Kolios G, Manolopoulos VG. Multi-omics integration to identify the genetic expression and protein signature of dilated and ischemic cardiomyopathy. *Front Cardiovasc Med*. 2023;10, 1115623. https://doi.org/10.3389/fcvm.2023.1115623. Published 2023 Feb 13. PMID: 36860278, PMCID: PMC9968758.
82. Russell-Hallinan A, Cappa O, Kerrigan L, et al. Single-cell RNA sequencing reveals cardiac fibroblast-specific transcriptomic changes in dilated cardiomyopathy. *Cells*. 2024;13(9):752. https://doi.org/10.3390/cells13090752. Published 2024 Apr 26. PMID: 38727290, PMCID: PMC11083662.
83. Yamaguchi T, Sumida TS, Nomura S, et al. Cardiac dopamine D1 receptor triggers ventricular arrhythmia in chronic heart failure. *Nat Commun*. 2020;11(1):4364. https://doi.org/10.1038/s41467-020-18128-x. Published 2020 Aug 31. PMID: 32868781, PMCID: PMC7459304.
84. Wang L, Yu P, Zhou B, et al. Single-cell reconstruction of the adult human heart during heart failure and recovery reveals the cellular landscape underlying cardiac function. *Nat Cell Biol*. 2020;22(1):108–119. https://doi.org/10.1038/s41556-019-0446-7. PMID: 31915373.
85. Koenig AL, Shchukina I, Amrute J, et al. Single-cell transcriptomics reveals cell-type-specific diversification in human heart failure. *Nat Cardiovasc Res*. 2022;1(3):263–280. https://doi.org/10.1038/s44161-022-00028-6. PMID: 35959412, PMCID: PMC9364913.
86. Chaffin M, Papangeli I, Simonson B, et al. Single-nucleus profiling of human dilated and hypertrophic cardiomyopathy. *Nature*. 2022;608(7921):174–180. https://doi.org/10.1038/s41586-022-04817-8. PMID: 35732739.
87. Reichart D, Lindberg EL, Maatz H, et al. Pathogenic variants damage cell composition and single cell transcription in cardiomyopathies. *Science*. 2022;377(6606). https://doi.org/10.1126/science.abo1984. eabo1984PMID: 35926050, PMCID: PMC9528698.
88. Ameen M, Sundaram L, Shen M, et al. Integrative single-cell analysis of cardiogenesis identifies developmental trajectories and non-coding mutations in congenital heart disease. *Cell*. 2022;185(26):4937–4953. https://doi.org/10.1016/j.cell.2022.11.028. e23PMID: 36563664, PMCID: PMC10122433.
89. Ampong I. Metabolic and metabolomics insights into dilated cardiomyopathy. *Ann Nutr Metab*. 2022;78(3):147–155. https://doi.org/10.1159/000524722. PMID: 35472668.
90. Garnier S, Harakalova M, Weiss S, et al. Genome-wide association analysis in dilated cardiomyopathy reveals two new players in systolic heart failure on chromosomes 3p25.1 and 22q11.23. *Eur Heart J*. 2021;42(20):2000–2011. https://doi.org/10.1093/eurheartj/ehab192. PMID: 33677556, PMCID: PMC813985310.1093/eurheartj/ehab030.
91. Verdonschot JAJ, Hazebroek MR, Krapels IPC, et al. Implications of genetic testing in dilated cardiomyopathy. *Circ Genom Precis Med*. 2020;13(5):476–487. https://doi.org/10.1161/CIRCGEN.120.003031. PMID: 32880476.
92. Vignoli A, Fornaro A, Tenori L, et al. Metabolomics fingerprint predicts risk of death in dilated cardiomyopathy and heart failure. *Front Cardiovasc Med*. 2022;9, 851905. https://doi.org/10.3389/fcvm.2022.851905. Published 2022 Apr 7. PMID: 35463749, PMCID: PMC9021397.
93. Asatryan B, Chahal CAA. Enhancing risk stratification for life-threatening ventricular arrhythmias in dilated cardiomyopathy: the peril and promise of precision medicine. *ESC Heart Fail*. 2020;7(4):1383–1386. https://doi.org/10.1002/ehf2.12886. PMID: 32643283, PMCID: PMC7373937.
94. Dal Ferro M, Stolfo D, Altinier A, et al. Association between mutation status and left ventricular reverse remodelling in dilated cardiomyopathy. *Heart*. 2017;103(21):1704–1710. https://doi.org/10.1136/heartjnl-2016-311017. PMID: 28416588.
95. Niskanen JE, Ohlsson Å, Ljungvall I, et al. Identification of novel genetic risk factors of dilated cardiomyopathy: from canine to human. *Genome Med*. 2023;15(1):73. https://doi.org/10.1186/s13073-023-01221-3. Published 2023 Sep 18. PMID: 37723491, PMCID: PMC10506233.
96. Burke MA, Cook SA, Seidman JG, Seidman CE. Clinical and mechanistic insights into the genetics of cardiomyopathy. *J Am Coll Cardiol*. 2016;68(25):2871–2886. https://doi.org/10.1016/j.jacc.2016.08.079. PMID: 28007147, PMCID: PMC5843375.
97. van Spaendonck-Zwarts KY, Posafalvi A, van den Berg MP, et al. Titin gene mutations are common in families with both peripartum cardiomyopathy and dilated cardiomyopathy. *Eur Heart J*. 2014;35(32):2165–2173. https://doi.org/10.1093/eurheartj/ehu050. PMID: 24558114.
98. García-Hernandez S, Iglesias LM. Genetic testing as a guide for treatment in dilated cardiomyopathies. *Curr Cardiol Rep*. 2022;24(11):1537–1546. https://doi.org/10.1007/s11886-022-01772-8. PMID: 35994197.
99. Sakellaropoulos SG, Baggish AL, Fifer MA, Lewis GD. Exercise oscillatory ventilation in hypertrophic cardiomyopathy. *Curr Probl Cardiol*. 2022;47(5), 100911. https://doi.org/10.1016/j.cpcardiol.2021.100911. MayEpub 2021 May 29. PMID: 34210521, DOI: 10.1016/j.cpcardiol.2021.100911.
100. Muchir A, Wu W, Choi JC, et al. Abnormal p38α mitogen-activated protein kinase signaling in dilated cardiomyopathy caused by lamin A/C gene mutation. *Hum Mol Genet*. 2012;21(19):4325–4333. https://doi.org/10.1093/hmg/dds265. PMID: 22773734, PMCID: PMC3441127.
101. Deiman FE, Bomer N, van der Meer P, Grote Beverborg N. Review: precision medicine approaches for genetic cardiomyopathy: targeting Phospholamban R14del. *Curr Heart Fail Rep*. 2022;19(4):170–179. https://doi.org/10.1007/s11897-022-00558-x. PMID: 35699837, PMCID: PMC9329159.
102. Romano R, Ghahremani S, Zimmerman T, et al. Reading frame repair of TTN truncation variants restores titin quantity and functions. *Circulation*. 2022;145(3):194–205. https://doi.org/10.1161/CIRCULATIONAHA.120.049997. PMID: 34905694, PMCID: PMC8766920.
103. Peters S, Thompson BA, Perrin M, et al. Arrhythmic phenotypes are a defining feature of dilated cardiomyopathy-associated SCN5A variants: a systematic review. *Circ Genom Precis Med*. 2022;15(1), e003432. https://doi.org/10.1161/CIRCGEN.121.003432. PMID: 34949099.
104. Ware JS, Cook SA. Role of titin in cardiomyopathy: from DNA variants to patient stratification. *Nat Rev Cardiol*. 2018;15(4):241–252. https://doi.org/10.1038/nrcardio.2017.190. PMID: 29238064.
105. Olivaes J, Bonamino MH, Markoski MM. CRISPR/Cas 9 system for the treatment of dilated cardiomyopathy: a hypothesis related to function of a MAP kinase. *Med Hypotheses*. 2019;128:91–93. https://doi.org/10.1016/j.mehy.2019.05.013. PMID: 31203918.

106. Ghahremani S, Kanwal A, Pettinato A, et al. CRISPR activation reverses haploinsufficiency and functional deficits caused by TTN truncation variants. *Circulation*. 2024;149(16):1285–1297. https://doi.org/10.1161/CIRCULATIONAHA.123.063972. PMID: 38235591, PMCID: PMC11031707.
107. El Refaey M, Xu L, Gao Y, et al. In vivo genome editing restores dystrophin expression and cardiac function in dystrophic mice. *Circ Res*. 2017;121(8):923–929. https://doi.org/10.1161/CIRCRESAHA.117.310996. PMID: 28790199, PMCID: PMC5623072.
108. Ganipineni VDP, Gutlapalli SD, Danda S, et al. Clustered regularly interspaced short palindromic repeats (CRISPR) in cardiovascular disease: a comprehensive clinical review on dilated cardiomyopathy. *Cureus*. 2023;15(3), e35774. https://doi.org/10.7759/cureus.35774. Published 2023 Mar 5. PMID: 37025725, PMCID: PMC10071452.
109. Dave J, Raad N, Mittal N, et al. Gene editing reverses arrhythmia susceptibility in humanized PLN-R14del mice: modelling a European cardiomyopathy with global impact. *Cardiovasc Res*. 2022;118(15):3140–3150. https://doi.org/10.1093/cvr/cvac021. PMID: 35191471, PMCID: PMC9732517.
110. Hakim CH, Wasala NB, Nelson CE, et al. AAV CRISPR editing rescues cardiac and muscle function for 18 months in dystrophic mice. *JCI Insight*. 2018;3(23), e124297. https://doi.org/10.1172/jci.insight.124297. Published 2018 Dec 6. PMID: 30518686, PMCID: PMC6328021.
111. Carrier L, Mearini G, Stathopoulou K, Cuello F. Cardiac myosin-binding protein C (MYBPC3) in cardiac pathophysiology. *Gene*. 2015;573(2):188–197. https://doi.org/10.1016/j.gene.2015.09.008. PMID: 26358504, PMCID: PMC6660134.
112. Gramlich M, Pane LS, Zhou Q, et al. Antisense-mediated exon skipping: a therapeutic strategy for titin-based dilated cardiomyopathy. *EMBO Mol Med*. 2015;7(5):562–576. https://doi.org/10.15252/emmm.201505047. PMID: 25759365, PMCID: PMC4492817.
113. van Mil A, Balk GM, Neef K, et al. Modelling inherited cardiac disease using human induced pluripotent stem cell-derived cardiomyocytes: progress, pitfalls, and potential. *Cardiovasc Res*. 2018;114(14):1828–1842. https://doi.org/10.1093/cvr/cvy208. PMID: 30169602, PMCID: PMC6887927.
114. Tse HF, Ho JC, Choi SW, et al. Patient-specific induced-pluripotent stem cells-derived cardiomyocytes recapitulate the pathogenic phenotypes of dilated cardiomyopathy due to a novel DES mutation identified by whole exome sequencing. published correction appears in Hum Mol Genet. 2014 Apr 15;23(8):2332-3 *Hum Mol Genet*. 2013;22(7):1395–1403. https://doi.org/10.1093/hmg/dds556. PMID: 23300193.
115. Perea-Gil I, Seeger T, Bruyneel AAN, et al. Serine biosynthesis as a novel therapeutic target for dilated cardiomyopathy. *Eur Heart J*. 2022;43(36):3477–3489. https://doi.org/10.1093/eurheartj/ehac305. PMID: 35728000, PMCID: PMC9794189.
116. Karakikes I, Stillitano F, Nonnenmacher M, et al. Correction of human phospholamban R14del mutation associated with cardiomyopathy using targeted nucleases and combination therapy. *Nat Commun*. 2015;6:6955. https://doi.org/10.1038/ncomms7955. Published 2015 Apr 29. PMID: 25923014, PMCID: PMC4421839.
117. Wyles SP, Hrstka SC, Reyes S, Terzic A, Olson TM, Nelson TJ. Pharmacological modulation of calcium homeostasis in familial dilated cardiomyopathy: an In vitro analysis from an RBM20 patient-derived iPSC model. *Clin Transl Sci*. 2016;9(3):158–167. https://doi.org/10.1111/cts.12393. PMID: 27105042, PMCID: PMC4902766.
118. Hinson JT, Chopra A, Nafissi N, et al. HEART DISEASE. Titin mutations in iPS cells define sarcomere insufficiency as a cause of dilated cardiomyopathy. *Science*. 2015;349(6251):982–986. https://doi.org/10.1126/science.aaa5458. PMID: 26315439, PMCID: PMC4618316.
119. Stillitano F, Turnbull IC, Karakikes I, et al. Genomic correction of familial cardiomyopathy in human engineered cardiac tissues. *Eur Heart J*. 2016;37(43):3282–3284. https://doi.org/10.1093/eurheartj/ehw307. PMID: 27450564, PMCID: PMC6425468.
120. Zhu L, Liu K, Feng Q, Liao Y. Cardiac organoids: a 3D technology for modeling heart development and disease. *Stem Cell Rev Rep*. 2022;18(8):2593–2605. https://doi.org/10.1007/s12015-022-10385-1. PMID: 35525908.
121. Lenneman CG, Sawyer DB. Cardio-oncology: an update on cardiotoxicity of cancer-related treatment. *Circ Res*. 2016;118(6):1008–1020. https://doi.org/10.1161/CIRCRESAHA.115.303633. PMID: 26987914.
122. Bolli R, Hare JM, Henry TD, et al. Rationale and design of the SENECA (StEm cell iNjECtion in cAncer survivors) trial. *Am Heart J*. 2018;201:54–62. https://doi.org/10.1016/j.ahj.2018.02.009. PMID: 29910056, PMCID: PMC7282462.
123. Parrillo JE, Cunnion RE, Epstein SE, et al. A prospective, randomized, controlled trial of prednisone for dilated cardiomyopathy. *N Engl J Med*. 1989;321(16):1061–1068. https://doi.org/10.1056/NEJM198910193211601. PMID: 2677721.
124. Müller J, Wallukat G, Dandel M, et al. Immunoglobulin adsorption in patients with idiopathic dilated cardiomyopathy. *Circulation*. 2000;101(4):385–391. https://doi.org/10.1161/01.cir.101.4.385. PMID: 10653829.
125. Frustaci A, Russo MA, Chimenti C. Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC study. *Eur Heart J*. 2009;30(16):1995–2002. https://doi.org/10.1093/eurheartj/ehp249. PMID: 19556262.
126. Wojnicz R, Nowalany-Kozielska E, Wojciechowska C, et al. Randomized, placebo-controlled study for immunosuppressive treatment of inflammatory dilated cardiomyopathy: two-year follow-up results. *Circulation*. 2001;104(1):39–45. https://doi.org/10.1161/01.cir.104.1.39. PMID: 11435335.
127. Van Tassell BW, Abouzaki NA, Oddi Erdle C, et al. Interleukin-1 blockade in acute decompensated heart failure: a randomized, double-blinded, placebo-controlled pilot study. *J Cardiovasc Pharmacol*. 2016;67(6):544–551. https://doi.org/10.1097/FJC.0000000000000378. PMID: 26906034, PMCID: PMC5749643.
128. Van Tassell BW, Canada J, Carbone S, et al. Interleukin-1 blockade in recently decompensated systolic heart failure: results from REDHART (Recently decompensated heart failure Anakinra response trial). *Circ Heart Fail*. 2017;10(11), e004373. https://doi.org/10.1161/CIRCHEARTFAILURE.117.004373. PMID: 29141858, PMCID: PMC5699505.
129. Mobini R, Staudt A, Felix SB, et al. Hemodynamic improvement and removal of autoantibodies against beta1-adrenergic receptor by immunoadsorption therapy in dilated cardiomyopathy. *J Autoimmun*. 2003;20(4):345–350. https://doi.org/10.1016/s0896-8411(03)00042-8. PMID: 12791320.
130. Gullestad L, Aass H, Fjeld JG, et al. Immunomodulating therapy with intravenous immunoglobulin in patients with chronic heart failure. *Circulation*. 2001;103(2):220–225. https://doi.org/10.1161/01.cir.103.2.220. PMID: 11208680.
131. Dörr M, Böhm M, Erdmann E, et al. Multicentre, randomized, double-blind, prospective study on the effects of ImmunoAdSorptiOn on cardiac function in patients with dilated CardioMyopathy (IASO-DCM): rationale and design. *Eur J Heart Fail*. 2024;2. https://doi.org/10.1002/ejhf.3476. Published online OctoberPMID: 39359033.
132. Heymans S, Eriksson U, Lehtonen J, Cooper Jr LT. The quest for new approaches in myocarditis and inflammatory cardiomyopathy. *J Am Coll Cardiol*. 2016;68(21):2348–2364. https://doi.org/10.1016/j.jacc.2016.09.937. PMID: 27884253.
133. Diaz-Navarro R, Urrútia G, Cleland JG, et al. Stem cell therapy for dilated cardiomyopathy. *Cochrane Database Syst Rev*. 2021;7(7), CD013433. https://doi.org/10.1002/14651858.CD013433.pub2. Published 2021 Jul 21. PMID: 34286511, PMCID: PMC8406792.
134. Kastrup, J., 2021. Stem cell therapy in non-IschEmic non-treatable dilated CardiomyopathiEs II: a pilot study. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT03797092.
135. Kertai MD, Fontes M, Podgoreanu MV. Pharmacogenomics of β-blockers and statins: possible implications for perioperative cardiac complications. *J Cardiothorac Vasc Anesth*. 2012;26(6):1101–1114. https://doi.org/10.1053/j.jvca.2012.06.025. PMID: 22889606.
136. Lennard MS, Silas JH, Freestone S, Ramsay LE, Tucker GT, Woods HF. Oxidation phenotype–a major determinant of metoprolol metabolism and response. *N Engl J Med*. 1982;307(25):1558–1560. https://doi.org/10.1056/NEJM198212163072505. PMID: 7144837.
137. Deroubaix X, Lins RL, Lens S, et al. Comparative bioavailability of a metoprolol controlled release formulation and a bisoprolol normal release tablet after single oral dose administration in healthy volunteers. *Int J Clin Pharmacol Ther*. 1996;34(2):61–70. PMID: 8929748.
138. Rysz J, Franczyk B, Rysz-Górzyńska M, Gluba-Brzózka A. Pharmacogenomics of hypertension treatment. *Int J Mol Sci*. 2020;21(13):4709. https://doi.org/10.3390/ijms21134709. Published 2020 Jul 1. PMID: 32630286, PMCID: PMC7369859.