

## **From Bench to Bedside: A Scoping Review of Gene Therapy Approaches in the Management of Cardiomyopathies**

### **Abstract**

**Background:** Cardiomyopathies represent a heterogeneous group of heart muscle diseases with diverse etiologies. With the advent of molecular biology and genetic engineering, novel therapeutic strategies are being developed and explored to target the genetic basis of these diseases.

**Methods:** A scoping review was performed of studies published between 2017 and 2023, exploring gene-based therapeutic interventions for various forms of cardiomyopathies. Literature was selected from a wide range of international databases, including PubMed, EMBASE, and Web of Science, with selection criteria focused on the application of gene therapies in preclinical and clinical studies.

**Findings:** A total of 9 studies were included in the review, revealing various gene therapy strategies, including antisense therapies, gene editing, miRNA manipulation, and the use of gene therapy vectors for targeted treatment. Although most of the studies were conducted in preclinical models, they exhibited promising outcomes such as improved cardiac function, reduced fibrosis, and amelioration of disease phenotype. The review also highlighted the considerable heterogeneity among studies in terms of the disease models used, targeted genes, and measured outcomes, indicating the complexity of the field.

**Conclusion:** This scoping review presents an overview of the emerging gene therapy strategies for cardiomyopathies, revealing promising outcomes in preclinical models. However, several challenges remain, including the translation of findings from animal models to humans, ethical considerations, and potential disparities in access to these treatments. Future research should focus on addressing these challenges to pave the way for innovative, efficacious, and accessible therapies for patients with cardiomyopathies.

**Keywords:** Cardiomyopathy, Gene Therapy, Preclinical Models, Antisense Therapies, Gene Editing

## Introduction

Cardiomyopathies are diseases characterized by myocardial dysfunction, with distinct pathological manifestations varying across different types (1–5). Hypertrophic cardiomyopathy (HCM) involves thickening of the heart muscle, particularly in the ventricles, often leading to obstructed blood flow and an increased risk of arrhythmias and sudden cardiac death (6). This is frequently linked to genetic mutations in sarcomeric proteins (7). On the other hand, dilated cardiomyopathy (DCM) is marked by the dilation and impaired contraction of one or both ventricles, with the thinned, weakened heart muscle struggling to effectively pump blood, leading to heart failure (8–11). DCM can be idiopathic, familial, or associated with various conditions such as myocarditis, alcoholism, or chemotherapy (12).

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by fibrofatty replacement of the myocardium, primarily affecting the right ventricle, and resulting in structural and electrical instability of the heart, which makes patients susceptible to ventricular arrhythmias and sudden cardiac death (13). Restrictive cardiomyopathy (RCM), however, occurs when the heart muscle becomes rigid, limiting the heart's ability to fill with blood and subsequently impairing its pumping function (14). The complexity and diversity of these pathologies, combined with the limited efficacy of traditional symptomatic treatments, have led to the exploration of novel therapeutic strategies, including gene and molecular pathway-targeted therapies (15). The understanding and unravelling of these complex interplays between genetics, molecular biology, and cellular processes are pivotal for advancing our knowledge of these diseases and the development of effective treatments.

Despite a growing understanding of the molecular and cellular mechanisms underpinning these conditions, developing effective treatments remains a challenge. Traditional therapeutic strategies for cardiomyopathies have largely focused on mitigating symptoms and preventing complications but are less effective in modifying disease progression or reversing pathological changes. This is further complicated by the diversity of etiologies and manifestations across different cardiomyopathy subtypes.

However, in the past decade, a new era of therapy has emerged with significant advancements in genetic and molecular medicine (16). This has opened up new opportunities for targeted therapies, aiming to address the underlying genetic or molecular defects. These include but are not limited to gene therapy, antisense oligonucleotide therapy, exon skipping techniques, and CRISPR-based gene-editing technologies. While these innovative approaches have shown promising results in preclinical models, their translation into clinical practice warrants a comprehensive understanding of their efficacy, safety, and feasibility.

The rapid pace of development in this field emphasizes the need for up-to-date and critical synthesis of the emerging evidence. This review aimed to synthesize the latest developments in targeted therapies for cardiomyopathies, providing a clear picture of the recent progress in this field and outlining areas where further research is needed. Through this scoping review, we

strive to foster a better understanding of these innovative treatments, contributing to the ongoing efforts towards improving the prognosis and quality of life of patients with cardiomyopathies.

## Methods

The methodology for this study was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) scoping review guidelines. The purpose of the study was to provide a comprehensive review of the most recent literature, with a particular focus on the last five years, to analyze the latest advancements in the specified field.

## Search Strategy

We began our study with a rigorous literature search that focused on the last five years of research. This temporal limitation was applied to ensure that the study incorporated the most recent and thus relevant findings. The databases PubMed, Scopus, Web of Science, and Google Scholar were systematically searched for relevant studies. Keywords and MeSH (Medical Subject Headings) terms related to the subject matter were used to conduct the search. The search was not limited by language or geographical location, and peer-reviewed articles were considered for inclusion.

The combinations are given as follows for all databases/search engines:

- **PubMed:** ("Preclinical experimental study" OR "Antisense oligonucleotide" OR "Micro-dystrophin gene therapy" OR "CRISPR/Cas9-AID (eTAM)" OR "Adeno-associated virus 9-mediated gene delivery" OR "CRISPR repair" OR "Cell-based and gene therapy" OR "Overexpression of SSPN" OR "Delivery of miR-21 via type 9 adeno-associated virus") AND ("cardiomyopathy" OR "heart failure" OR "cardiac").
- **Scopus:** (TITLE-ABS-KEY("Preclinical experimental study") OR TITLE-ABS-KEY("Antisense oligonucleotide") OR TITLE-ABS-KEY("Micro-dystrophin gene therapy") OR TITLE-ABS-KEY("CRISPR/Cas9-AID (eTAM)") OR TITLE-ABS-KEY("Adeno-associated virus 9-mediated gene delivery") OR TITLE-ABS-KEY("CRISPR repair") OR TITLE-ABS-KEY("Cell-based and gene therapy") OR TITLE-ABS-KEY("Overexpression of SSPN") OR TITLE-ABS-KEY("Delivery of miR-21 via type 9 adeno-associated virus")) AND (TITLE-ABS-KEY("cardiomyopathy") OR TITLE-ABS-KEY("heart failure") OR TITLE-ABS-KEY("cardiac"))
- **Web of Science:** (TS=("Preclinical experimental study") OR TS=("Antisense oligonucleotide") OR TS=("Micro-dystrophin gene therapy") OR TS=("CRISPR/Cas9-AID (eTAM)") OR TS=("Adeno-associated virus 9-mediated gene delivery") OR TS=("CRISPR repair") OR TS=("Cell-based and gene therapy") OR TS=("Overexpression of SSPN") OR TS=("Delivery of miR-21 via type 9 adeno-associated virus")) AND (TS=("cardiomyopathy") OR TS=("heart failure") OR TS=("cardiac"))

- **Google Scholar:** "Preclinical experimental study" OR "Antisense oligonucleotide" OR "Micro-dystrophin gene therapy" OR "CRISPR/Cas9-AID (eTAM)" OR "Adeno-associated virus 9-mediated gene delivery" OR "CRISPR repair" OR "Cell-based and gene therapy" OR "Overexpression of SSPN" OR "Delivery of miR-21 via type 9 adeno-associated virus" AND "cardiomyopathy" OR "heart failure" OR "cardiac"

## Study Selection

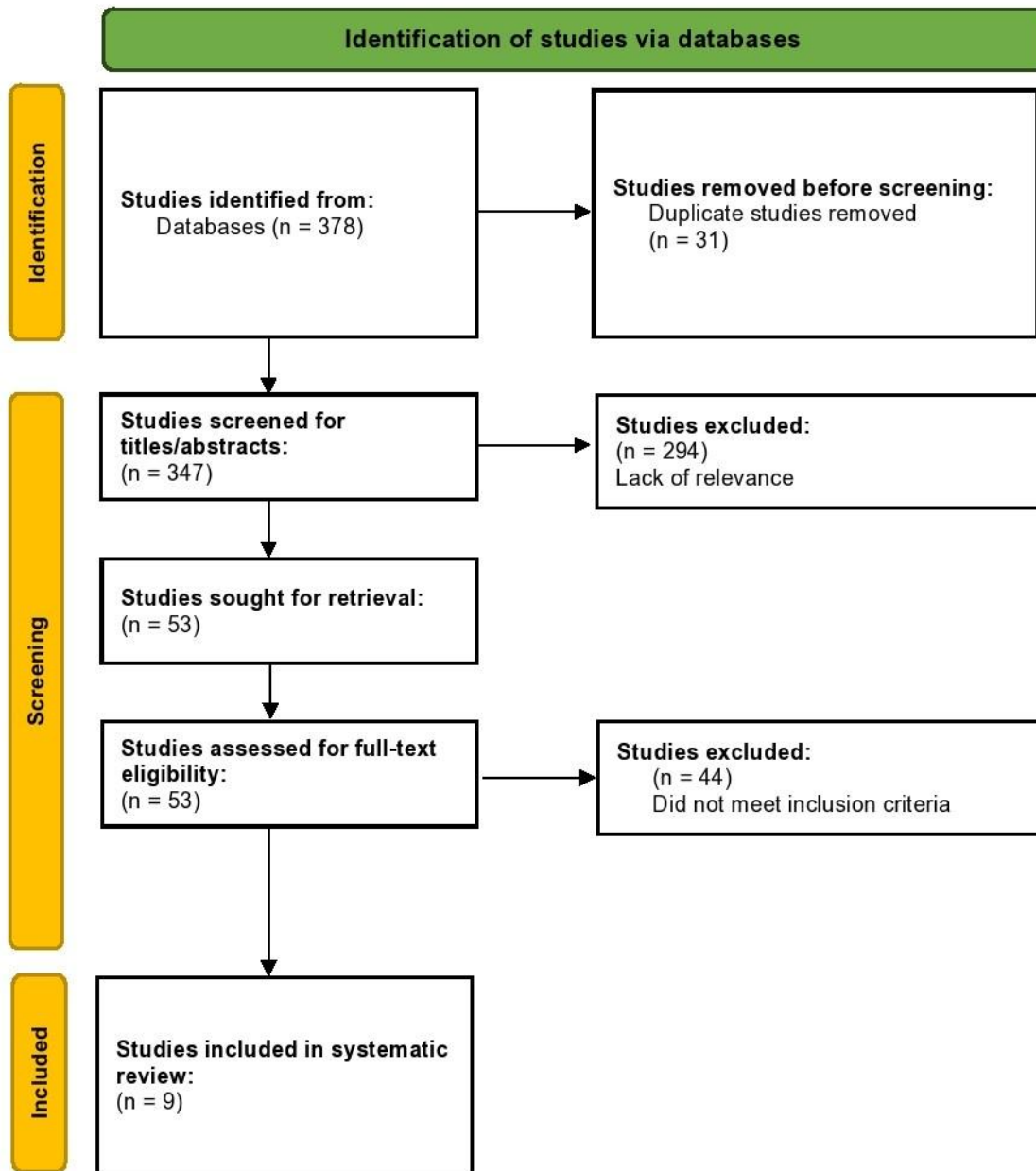
The initial search results were independently screened by two researchers for relevance based on titles and abstracts. Any discrepancies were resolved through discussion or consultation with a third researcher. The full texts of the shortlisted articles were then obtained and further scrutinized for eligibility. The studies were included if they met the following criteria: original research studies published in the last five years, studies focusing on the specified subject matter, and studies providing sufficient data for extraction and analysis.

## Data Extraction and Synthesis

Data from the included studies were systematically extracted by the research team. The data extracted included: author names, year of publication, study design, study objective, animal or cell model used (if applicable), intervention type, and key findings. The extracted data were then synthesized and analyzed qualitatively. The key findings were collated and summarized, and the results were categorized based on the study objectives, type of intervention, and animal or cell model used, to provide an overview of the research landscape. The synthesis also highlighted the potential impact of these studies on the field and identified gaps in the existing research.

## Results

Of the 378 studies identified, a total of 53 were reviewed with full-texts. Of these 9 studies were included in this scoping review. The PRISMA flowchart depicting the study selection process is presented in Figure 1.



**Figure 1.** PRISMA flowchart depicting the study selection process.

Table 1 depicts the layman summary of the studies in this scoping review. Table 2 presents the key characteristics of the included studies.

**Table 1.** Layman summaries of the studies included in this scoping review.

Author, Year	Layman Summary
Eijgenraam, 2022	Researchers tested a genetic therapy (called PLN-targeting antisense oligonucleotide or ASO) on mice with a specific type of heart disease. They found that this therapy was able to halt the disease from getting worse, improve heart function, and extend the lifespan of the mice.
Beverborg, 2021	This study looked at the use of a genetic therapy called antisense oligonucleotides (ASOs) in mice with heart failure. They discovered that this treatment could prevent the build-up of harmful proteins in the heart, improve the heart's function, and increase the survival rate of the mice.
Howard, 2021	In this study, the scientists investigated a type of gene therapy in a mouse model of Duchenne muscular dystrophy, a serious muscle-wasting disease. They found that this therapy could prevent the heart from failing and stop inflammation and scarring from developing in the heart.
Li, 2021	The researchers tested a gene-editing tool (CRISPR/Cas9-AID or eTAM) to treat a type of heart disease in mice. They used this tool to skip a problematic part of a gene. As a result, they restored the heart's function, improved muscle function, and increased the lifespan of the mice.
Hall, 2020	Scientists studied how a specific protein, PRMT5, helps to maintain the normal functioning of the heart in mice. They discovered that a type of gene therapy could help correct the problems caused by the lack of PRMT5, improving the heart's function.
Hanses, 2020	This research focused on understanding a type of heart disease (hypertrophic cardiomyopathy) associated with Noonan Syndrome (a genetic disorder). Using human heart cells grown in the lab, they found a new link between the dysfunction of a particular gene (LZTR1) and heart cell enlargement. They also showed that using the gene-editing tool CRISPR to repair the mutation was able to reverse the heart cell enlargement.
Sant'Anna, 2020	This Brazilian research group shared their experience with using cell-based and gene therapy to treat two types of heart disease. While they found these therapies promising in their lab experiments, they noted that these positive results did not transfer as well to patients in the clinic.
Parvatiyar, 2019	This study tested a treatment strategy for Duchenne Muscular Dystrophy, a genetic disorder that often leads to heart disease. The treatment involved increasing the production of a protein called sarcospan (SSPN) in mice. They found that this treatment stabilized the heart cell membranes, reduced scarring, and improved the heart's ability to contract.
Dai, 2018	A molecule called miR-21 was found to alleviate heart disease in diabetic mice, suggesting a new approach for treatment.

**Abbreviations:** ASO: PLN-targeting antisense oligonucleotide; HD: Heart disease; GT: Genetic therapy; ASOs: Antisense oligonucleotides; HF: Heart failure; DMD: Duchenne muscular dystrophy; CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats; PRMT5: Protein Arginine Methyltransferase 5; NS: Noonan Syndrome; HCM: Hypertrophic; CBT: Cell-based therapy; DMD: Duchenne Muscular Dystrophy; SSPN: Sarcospan; miR-21: microRNA-21.

**Table 2.** Characteristics of the Included Studies.

Author, Year	Title	Study Design	Objective/Purpose	Animal/Cell Model Used (if applicable)	Intervention	Key Findings
Eijgenraam, 2022	Antisense Therapy Attenuates Phospholamban p.(Arg14del) Cardiomyopathy in Mice and Reverses Protein Aggregation	Preclinical experimental study	To investigate if administration of a PIn-targeting antisense oligonucleotide (ASO) could halt or reverse disease progression in mice with advanced PLN-R14del cardiomyopathy	Mice with advanced PLN-R14del cardiomyopathy	PLN-targeting antisense oligonucleotide (ASO) injections	PLN-ASO therapy halted further cardiac remodeling and dysfunction, extending lifespan, and resolved PLN aggregates

Beverborg, 2021	Phospholamban antisense oligonucleotides improve cardiac function in murine cardiomyopathy	Preclinical experimental study	To investigate the efficacy of antisense oligonucleotides (ASOs) in interfering with the PLN/SERCA2a interaction and downregulating Pln mRNA in the heart of murine HF models	Mice with PLN R14del variant and Cspr3/Mip <sup>-/-</sup> variant; Rats with myocardial infarction	Antisense oligonucleotides (ASOs)	Antisense inhibition of PLN prevented PLN protein aggregation, cardiac dysfunction, increased survival rate, and reversed the HF phenotype in preclinical models
Howard, 2021	Micro-dystrophin gene therapy prevents heart failure in an improved Duchenne muscular dystrophy cardiomyopathy mouse model	Preclinical experimental study	To investigate the effect of micro-dystrophin gene therapy on prevention of heart failure in DMD mouse model	DMD mouse model	Micro-dystrophin gene therapy	Micro-dystrophin prevented declines in cardiac function and prohibited onset of inflammation and fibrosis
Li, 2021	Therapeutic Exon Skipping Through a CRISPR-Guided Cytidine Deaminase Rescues Dystrophic Cardiomyopathy in Vivo	Preclinical experimental study	To test the feasibility of using a cytidine base editor to install exon skipping and rescue dystrophic cardiomyopathy in a novel murine model of DMD	Novel murine model of DMD with a 4-bp deletion into exon 4	CRISPR/Cas9-AID (eTAM) together with AAV9-sgRNA	AAV9-eTAM induced targeted exon skipping in the Dmd transcripts, restored up to 90% dystrophin in the heart, improved cardiac and skeletal muscle functions, increased lifespan of the DmdE4* mice
Hall, 2020	RNA sequencing-based transcriptome profiling of cardiac tissue implicates novel putative disease mechanisms in FLNC-associated arrhythmogenic cardiomyopathy	Preclinical experimental study	To elucidate the physiological function of PRMT5 and the mechanism underlying its role in regulating cardiac O-GlcNAcylation and homeostasis	PRMT5-knockout mice	Adeno-associated virus 9-mediated gene delivery	PRMT5 regulates protein O-GlcNAcylation to maintain cardiac homeostasis; gene therapy with adeno-associated virus 9 encoding the correctly spliced Oga normalized the cardiac protein O-GlcNAcylation levels and partially rescued the dilation and dysfunction of the hearts in PRMT5-knockout mice
Hanses, 2020	Intronic CRISPR Repair	Observational, Case-Control	To explore the mechanism of	Human Induced pluripotent stem	CRISPR repair	Revealed a new link between

	in a Preclinical Model of Noonan Syndrome-Associated Cardiomyopathy		Noonan syndrome (NS) associated hypertrophic cardiomyopathy and find effective therapeutic options.	cell-derived cardiomyocytes (from NS patients)		LZTR1 dysfunction, RAS-MAPK signaling hyperactivity, and cellular hypertrophy. CRISPR repair was able to reverse the hypertrophic phenotype.
Sant'Anna, 2020	Gene therapy for refractory angina and cell therapy for heart failure: experience of a Brazilian research group	Observational, Case Series & Review	To report and review the findings of cell-based and gene therapy methods in the treatment of dilated and ischemic cardiomyopathies.	Human & animal models (Not specified in the extract)	Cell-based and gene therapy	Benefits of cell-based and gene therapy observed in preclinical trials but poor translation to clinical level.
Parvatiyar, 2019	Stabilization of the cardiac sarcolemma by sarcospan rescues DMD-associated cardiomyopathy	Preclinical Experimental	To demonstrate the therapeutic potential of sarcospan (SSPN) overexpression to alleviate DMD-associated cardiomyopathy.	Dystrophin-deficient mdx mice with utrophin haploinsufficiency	Overexpression of SSPN	SSPN restored cardiac sarcolemma stability, reduced fibrotic response, and improved contractile function.
Dai, 2018	MiR-21 protected against diabetic cardiomyopathy induced diastolic dysfunction by targeting gelsolin	Preclinical Experimental	To investigate the role of miR-21 in diabetic cardiomyopathy and its potential as a therapeutic target.	Leptin receptor-deficient (db/db) mice, primary cardiomyocytes and cardiomyocyte cell lines	Delivery of miR-21 via type 9 adeno-associated virus and cardiac Troponin T promoter	Delivery of miR-21 attenuated diabetic cardiomyopathy by reducing ROS production, increasing bioavailable NO, and relieving cardiomyocyte hypertrophy.

**Abbreviations:** ASO: Antisense oligonucleotide; HD: Heart disease; PLN: Phospholamban; R14del: p.(Arg14del) variant; HF: Heart failure; mRNA: Messenger RNA; Cspr3/Mlp-/-: Calsequestrin 3/Muscle LIM protein knockout variant; PLN-ASO: PLN-targeting antisense oligonucleotide; AAV9: Adeno-associated virus 9; DMD: Duchenne muscular dystrophy; Dmd: Dystrophin gene; CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats; Cas9-AID: Cas9-Activation-Induced Cytidine Deaminase; eTAM: Exon Targeting with Activation-Induced Cytidine Deaminase; AAV9-sgRNA: Adeno-associated virus 9-small guide RNA; O-GlcNAcylation: O-linked N-acetylglucosaminylation; PRMT5: Protein Arginine Methyltransferase 5; FLNC: Filamin C; LZTR1: Leucine zipper-like transcription regulator 1; RAS-MAPK: RAS-mitogen-activated protein kinase; NS: Noonan syndrome; CRISPR repair: CRISPR-based genetic repair; RAS: Rat sarcoma; MAPK: Mitogen-activated protein kinase; RNA: Ribonucleic acid; DMD-associated: Duchenne muscular dystrophy-associated; SSPN: Sarcospan; ROS: Reactive oxygen species; NO: Nitric oxide

In a study by Eijgenraam (2022), an antisense therapy was developed to target a specific variant of a protein (PLN) involved in cardiomyopathy (17). When this therapy was given to mice with advanced PLN-related cardiomyopathy, the disease progression was halted. The treatment prevented further heart abnormalities and dysfunction, extended the animals' lifespan, and even resolved harmful protein aggregates that had formed due to the disease.

Similar to the Eijgenraam study, Beverborg (2021) used antisense oligonucleotides (ASOs), a type of genetic therapy, to interfere with the interaction between PLN and another protein (SERCA2a) (18). In mice models with heart failure, this intervention prevented PLN protein aggregation, cardiac dysfunction, and also reversed the heart failure phenotype, leading to an increased survival rate.

Micro-dystrophin gene therapy was the focus of a study by Howard (2021), conducted on a mouse model of Duchenne muscular dystrophy (DMD), a genetic disorder that causes progressive muscle degeneration (19). The results showed that the therapy was successful in preventing declines in cardiac function and in preventing the onset of inflammation and fibrosis, which are usually observed in this disease.

Li (2021) used a different approach, employing a specific type of CRISPR gene editing system to induce "exon skipping," a process that can bypass mutations in genes (20). In mice models of DMD with a specific mutation, this intervention restored up to 90% of the dystrophin protein (which is typically missing or defective in DMD) in the heart. It also improved cardiac and skeletal muscle functions and increased the lifespan of the affected mice.

Hall (2020) utilized RNA sequencing to understand the role of a protein called PRMT5 in cardiac homeostasis (21). Using mice with a knockout of the PRMT5 gene, they found that PRMT5 regulates a specific protein modification (O-GlcNAcylation) to maintain cardiac health. A gene therapy approach partially rescued the dilation and dysfunction observed in these PRMT5-knockout mice.

The study conducted by Hanses (2020) explored the mechanism of hypertrophic cardiomyopathy, a type of heart disease associated with Noonan Syndrome, a genetic disorder (22). Using human heart cells derived from patients with Noonan Syndrome, they found a link between a specific gene's dysfunction and cell enlargement. They used CRISPR gene editing to repair the gene and were able to reverse the enlargement.

Sant'Anna (2020) reported on the experience of a Brazilian research group using cell-based and gene therapies to treat dilated and ischemic cardiomyopathies (23). While the therapies showed promise in preclinical trials, they noted a gap in translating these findings to the clinical level.

In the Parvatiyar (2019) study, overexpression of a protein called sarcospan (SSPN) was used as a potential therapy for DMD-associated cardiomyopathy (24). They found that SSPN overexpression improved the stability of heart cell membranes, reduced scarring, and enhanced heart contractile function in a mouse model of DMD.

Lastly, the study by Dai (2018) focused on the role of miR-21 in diabetic cardiomyopathy, a heart condition associated with diabetes (25). They used a gene therapy approach to deliver miR-21 to diabetic mice, which helped to protect the heart from damage by reducing harmful reactive oxygen species, increasing beneficial nitric oxide, and relieving heart cell enlargement.

## Discussion

The studies outlined above provide a clear indication of the innovative and dynamic nature of therapeutic research in the field of cardiomyopathies. These results are suggestive of advances in molecular biology and have brought forth promising interventions for cardiomyopathies. For instance, Eijgenraam (2022) and Beverborg (2021) utilized antisense oligonucleotides (ASOs) to target the PLN protein variant, successfully halting or reversing disease progression in mouse models. Eijgenraam's study notably halted further cardiac remodeling and dysfunction and even dissolved previously formed PLN aggregates. Beverborg's intervention specifically interfered with the PLN/SERCA2a interaction, successfully preventing protein aggregation, cardiac dysfunction, and reversing heart failure phenotypes in mice. Other innovative therapies have also been investigated. Howard (2021) utilized micro-dystrophin gene therapy to prevent cardiac function decline and the onset of inflammation and fibrosis in a DMD mouse model. Similarly, Li (2021) utilized a CRISPR gene editing system to restore up to 90% of the dystrophin protein in DMD mouse models, which significantly improved cardiac and skeletal muscle functions. Hall (2020) elucidated PRMT5's role in cardiac health, revealing its regulation of O-GlcNAcylation and the potential of gene therapy as an intervention. Hanses (2020) explored the genetic basis of Noonan Syndrome-associated hypertrophic cardiomyopathy, identifying a potential therapeutic target and reversing the hypertrophic phenotype using CRISPR repair. Sant'Anna (2020) pointed out the translational challenges in applying cell-based and gene therapies from preclinical models to human patients. Parvatiyar (2019) showed that sarcospan (SSPN) overexpression can alleviate DMD-associated cardiomyopathy. Finally, Dai (2018) highlighted miR-21's potential in diabetic cardiomyopathy therapy, demonstrating its protective effects on cardiac cells in diabetic mouse models.

The success observed in preclinical models, such as that achieved by Eijgenraam (2022) and Beverborg (2021) using antisense oligonucleotides, or Li (2021) employing CRISPR-based gene-editing techniques, indicates potential strides toward treating these conditions at a genetic level. Notably, this exploration of the interplay between genetic therapies and the molecular basis of cardiomyopathies mirrors current trends in research beyond the scope of this review (1,26,27).

However, it is crucial to consider the translation of these findings to the clinical setting. Sant'Anna (2020) pointed out the difficulties in moving from preclinical models to human patients, reflecting a broader issue within biomedical research. Current therapies primarily aim to mitigate symptoms and prevent complications but have limited impact on disease progression or reversal (28). The diversity of manifestations across different cardiomyopathy subtypes adds complexity to developing universally effective treatments. The capacity of gene therapies to target specific genetic or molecular defects offers a promising approach to this issue (21).

Comparison of these findings to existing literature underscores the novelty and potential of these approaches. Antisense oligonucleotide therapy, as investigated by Eijgenraam (2022) and

Beverborg (2021), has emerged as a viable strategy for managing cardiomyopathies (22). Similarly, studies like that of Li (2021) and Hanses (2020) highlight the potential of CRISPR/Cas9 technologies in addressing the root cause of genetic diseases. The role of proteins such as PRMT5 (Hall, 2020) and Sarcospan (Parvatiyar, 2019) in maintaining cardiac health also reflects ongoing research trends (23,24).

Overall, these studies collectively represent a shift towards more precise, targeted therapies in cardiomyopathies that aim to address underlying genetic and molecular defects. As noted by Dai (2018), such strategies can potentially offer new treatments for cardiomyopathies associated with other conditions, such as diabetes.

However, these novel therapeutic strategies are still in the experimental stage. Although promising, their translation to the clinical setting requires thorough understanding and further investigation. Future research needs to focus not only on the efficacy but also on the safety, feasibility, and potential ethical considerations of these therapies (25). Indeed, as we strive to bridge the gap between preclinical findings and clinical application, it is vital to navigate these developments with a critical and scientifically robust approach.

Despite the promise of these new approaches, it is crucial to consider the complexity of the pathophysiological processes underlying cardiomyopathies. It is not simply a matter of defective genes; environmental factors, lifestyle choices, and other co-morbidities may also contribute to disease development and progression (29). While gene therapies can target specific genetic abnormalities, they might not address these multifactorial influences, hence the necessity for a comprehensive therapeutic approach that also includes lifestyle modifications and the management of other health conditions.

In addition to these considerations, the ethical implications and acceptability of gene-editing technologies, such as those used by Li (2021), cannot be understated. The use of such powerful tools requires careful regulation and extensive public dialogue to ensure their use is aligned with societal values and expectations. We must also consider the disparities in access to these innovative treatments that are likely to occur due to economic barriers or healthcare inequities (30).

### **Limitations and Strengths**

Although the studies discussed present promising findings, there are limitations to this scoping review that need to be considered. Most importantly, the studies included are predominantly preclinical and used animal models of disease, which might not fully replicate human pathophysiology. Additionally, the included studies are highly heterogeneous in terms of their interventions and outcomes, making it challenging to draw comprehensive conclusions. Lastly, the use of different cell or animal models across studies also introduces another level of complexity and potential bias in the interpretation of results.

One of the strengths of this scoping review is its wide range of included studies, which capture different aspects of the therapeutic interventions for cardiomyopathies, from antisense therapy to gene editing. It encompasses different types of heart diseases and a variety of animal and cell models, providing a broad overview of the current state of research in this field. Furthermore, the studies included used rigorous methodologies and innovative technologies, bolstering the credibility of their findings.

### **Future Recommendations**

Future research should focus on addressing the challenges in translating the success of these therapies in preclinical trials to the clinical level. This includes optimizing the delivery methods of gene therapies, ensuring their safety and efficacy in human trials, and investigating long-term outcomes (31,32). Furthermore, more studies are needed to explore the impacts of lifestyle and environmental factors on the effectiveness of these therapies. Finally, as these therapies are being developed, there should be parallel efforts to address the ethical, social, and economic considerations that come with these novel treatments.

### **Conclusion**

This scoping review provides an overview of the advances in the therapeutic strategies for cardiomyopathies, with a particular focus on gene therapies. The studies included demonstrate promising results in preclinical trials, using various approaches to target the genetic bases of different forms of heart disease. However, significant challenges remain in translating these findings to clinical applications, including the complexity of the diseases, ethical considerations, and potential disparities in access to these innovative treatments. Despite these challenges, the reviewed studies represent significant strides towards improving the outcomes and quality of life for patients with cardiomyopathies. The future of this field lies in the ability to combine these innovative treatments with traditional symptom management and lifestyle interventions. As the field progresses, it will be vital to address the ethical and societal implications of these powerful technologies and ensure equitable access to these potential life-saving treatments.

### **Glossary of Terms for The Layman:**

1. **Antisense Oligonucleotides (ASOs):** Short DNA or RNA molecules used in genetic therapy to control gene activity. They can turn off the production of a specific protein.
2. **Cardiomyopathy:** A disease of the heart muscle that makes it harder for the heart to pump blood to the rest of the body.
3. **Duchenne Muscular Dystrophy (DMD):** A genetic disorder characterized by progressive muscle degeneration and weakness due to the alterations of a protein called dystrophin that helps keep muscle cells intact.
4. **CRISPR/Cas9-AID (eTAM):** A gene-editing tool used to change the DNA of a cell in a specific way.

5. **Exon Skipping:** A strategy to bypass mutations in genes. It involves removing (or "skipping") sections of genetic material so that the body can still make a working protein.
6. **PRMT5:** A protein involved in many cellular processes, including the copying of DNA, the production of proteins, and the regulation of various signaling pathways.
7. **Noonan Syndrome:** A genetic disorder that prevents normal development in various parts of the body. It can lead to heart defects, short stature, learning disabilities, and other health problems.
8. **Sarcospan (SSPN):** A protein that helps stabilize the cell membrane of muscle cells.
9. **miR-21:** A type of small RNA molecule known as microRNA (miRNA) that has a role in regulating gene expression.
10. **Hypertrophic Cardiomyopathy:** A disease where the heart muscle becomes abnormally thick, making it harder for the heart to pump blood.
11. **RNA Sequencing:** A technology that can look at the quantity and sequences of RNA (a molecule similar to DNA) in a sample, allowing researchers to see what genes are being actively expressed.
12. **Diabetic Cardiomyopathy:** A disease that develops in some people who have been diabetic for several years. It can cause heart failure and arrhythmias even in the absence of coronary artery disease.
13. **Fibrosis:** The thickening and scarring of connective tissue, usually as a result of injury.
14. **Reactive Oxygen Species (ROS):** Chemically reactive chemical species containing oxygen. In excess, they can damage cell structures, but they also play a key role in cell signaling.
15. **Inflammation:** A process by which the body's white blood cells and the substances they produce protect us from infection with foreign organisms, such as bacteria and viruses.
16. **Phenotype:** The set of observable characteristics of an individual resulting from the interaction of its genotype (set of genes) with the environment.

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