Concept Paper

A Translational Framework for Target Validation in Genetic Cardiomyopathy

Sanghati Basu * and Prakash Narayan

Posted Date: 26 March 2026

doi: 10.20944/preprints202603.2164.v1

Keywords: hypertrophic cardiomyopathy; dilated cardiomyopathy; sarcomere; molecular stability; cross-cohort reproducibility; multi-omics; target validation; translational framework; concordance scoring; biomarkers

 doi:10.20944/preprints202603.2164.v1

Concept Paper

A Translational Framework for Target Validation in Genetic Cardiomyopathy

Sanghati Basu [1,*] and Prakash Narayan [2]

[1] Management Information Systems, University of Illinois, One University Plaza, UHB 4093 Springfield, Illinois 62703, USA

[2] Nodes and Edges LLC, 4030 Wake Forest Rd, Ste 349, Raleigh, NC 27609, USA

* Correspondence: sbasu23@uis.edu

Abstract

Genetic cardiomyopathies, encompassing hypertrophic cardiomyopathy and dilated cardiomyopathy, represent two of the most extensively characterized inherited cardiovascular disorders. Despite decades of mechanistic insight into sarcomeric dysfunction, calcium handling abnormalities, stress-responsive signaling cascades, and fibrotic remodeling, the translation of this knowledge into durable therapeutic success has remained uneven. A central but underappreciated challenge is the assumption that clinical pathogenicity inherently confers molecular stability that a variant classified as pathogenic will produce consistent downstream molecular perturbations across independent patient cohorts, disease stages, and biological contexts. We examine genetic cardiomyopathy biology through a translational lens, arguing that molecular stability and cross-cohort reproducibility must function as explicit development gates alongside mechanistic plausibility. We synthesize evidence across sarcomeric biology, calcium signaling, fibrosis, metabolic remodeling, and immune crosstalk, and critically appraise how biological heterogeneity, incomplete penetrance, and model limitations introduce translational risk. The expanding roles of multi-omics platforms and artificial intelligence-driven discovery are evaluated for both their promise and methodological fragility. Based on the available data and prevailing practices, a seven-step structured translational framework is proposed, operationalized through a five-domain Molecular Concordance Scoring Matrix that translates stability assessment into a scored, development-ready criterion. By reframing stability as a property of mechanism rather than a statistical afterthought, this framework aims to reduce late-stage development failure, improve biomarker reliability, and align therapeutic platform selection with the biological realities of genetically complex cardiac disease.

Keywords: hypertrophic cardiomyopathy; dilated cardiomyopathy; sarcomere; molecular stability; cross-cohort reproducibility; multi-omics; target validation; translational framework; concordance scoring; biomarkers

1. Introduction

Genetic cardiomyopathies represent one of the most intensively studied domains in cardiovascular medicine. Over the past three decades, advances in human genetics have transformed hypertophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM) from clinicopathologic syndromes into molecularly defined diseases. Pathogenic variants in sarcomeric genes such as ß-myosin heavy chain (MYH7) and myosin-binding protein C (MYBPC3) account for the majority of HCM cases [1], while truncating variants in titin (TTN) stand among the most common genetic contributors to DCM [2]. These discoveries have reshaped diagnostic strategies, informed cascade family screening, and opened the door to mechanism-directed therapies.

Despite this progress, the translation of genetic insight into durable therapeutic success has been uneven. While sarcomere-modulating agents have demonstrated clinical efficacy in obstructive HCM [3], many targets grounded in plausible signaling biology have failed to progress through late-stage

 doi:10.20944/preprints202603.2164.v1

development or have yielded inconsistent clinical signals. The persistent gap between mechanistic discovery and therapeutic durability suggests that variant identification alone is insufficient to guarantee translational readiness.

A central and underappreciated challenge lies in the complexity of genotype-phenotype relationships. Although HCM and DCM are frequently described as monogenic disorders, penetrance and expressivity vary substantially across individuals carrying the same primary mutation. Common genetic variants and modifiable environmental factors influence disease susceptibility and severity [4]. This variability extends beyond clinical phenotype to molecular expression patterns. Pathway activation states, fibrotic burden, metabolic remodeling, and inflammatory signatures may differ across cohorts stratified by age, hemodynamic load, comorbidities, or therapeutic exposure. Pathway activation observed in one cohort may therefore reflect compensatory remodeling or context-specific biology rather than universal disease drivers.

The emergence of multi-omics technologies has further expanded the mechanistic landscape. Transcriptomics, proteomics, metabolomics, and circulating biomarker platforms promise refined phenotyping and target discovery [5]. AI-driven integrative analyses seek to uncover latent disease subtypes and prioritize druggable nodes [6]. Yet high-dimensional datasets introduce new vulnerabilities. Signals identified in single cohorts may not generalize across populations or analytic pipelines. Exosomal biomarker discovery is highly sensitive to pre-analytic variation and workflow differences, complicating reproducibility [7]. Absent explicit validation across independent datasets, mechanistic conclusions risk being cohort-specific rather than disease-defining.

HCM and DCM represent two of the most common inherited cardiac disorders and are major contributors to heart failure, arrhythmia, and sudden cardiac death worldwide. HCM affects approximately 1 in 500 individuals globally, though contemporary genetic screening studies suggest prevalence may be closer to 1 in 200 when genotype-positive individuals are included. DCM has an estimated prevalence of approximately 1 in 250–500 individuals and accounts for a substantial proportion of non-ischemic heart failure and heart transplantation cases. In the United States, cardiomyopathies collectively contribute to hundreds of thousands of heart failure hospitalizations annually, with heart failure–related healthcare expenditures exceeding $30–40 billion per year, a portion of which is attributable to inherited and non-ischemic cardiomyopathies. Globally, heart failure and cardiomyopathy-related conditions represent a major and growing healthcare burden, with worldwide heart failure costs estimated to exceed $100 billion annually [8]. Individuals at highest risk include those with pathogenic sarcomeric variants, titin truncating variants, laminopathies, family history of cardiomyopathy or sudden cardiac death, exposure to cardiotoxic chemotherapy, viral myocarditis, pregnancy-related cardiomyopathy risk, and metabolic comorbidities such as diabetes and hypertension that modify penetrance and disease severity. Despite advances in genetic diagnosis and mechanistic understanding, cardiomyopathies remain a major cause of morbidity, mortality, and healthcare expenditure, highlighting the need for improved translational frameworks to move mechanistic discoveries into durable therapeutic strategies. We posit that a structured framework will bridge genetic discovery and development execution. Target validation in genetic cardiomyopathy must extend beyond variant association and mechanistic plausibility to include systematic evaluation of cross-cohort reproducibility, biomarker stability, model fidelity, and modality alignment. Stability should be treated as a property of mechanism. Concordance should function as a development gate.

2. Methods

We conducted a structured narrative synthesis with systematic search elements. The objective was not to generate pooled effect estimates but to critically evaluate translational evidence across mechanistic, biomarker, and therapeutic domains in genetic cardiomyopathies, with emphasis on studies incorporating mechanistic mapping, reproducibility considerations, and clinical or development relevance.

 doi:10.20944/preprints202603.2164.v1

A structured query was performed across PubMed/MEDLINE, Web of Science, Scopus, Embase, and ClinicalTrials.gov. Search terms included combinations of "hypertrophic cardiomyopathy," "dilated cardiomyopathy," "sarcomere mutation," specific gene identifiers (MYH7, MYBPC3, TTN), key signaling pathway terms (calcineurin- Nuclear Factor of Activated T-cells (NFAT), cardiac remodeling, fibrosis), multi-omics platforms (proteomics, metabolomics, exosomes), and translational concepts (reproducibility, molecular stability, biomarker qualification, genome editing). The initial search identified approximately 1,840 potentially relevant records. Following title and abstract screening for mechanistic or translational relevance, 312 full-text articles were assessed for eligibility. Of these, 18 were selected as primary citations based on mechanistic specificity, human validation, cross-cohort relevance, or direct therapeutic significance. Earlier seminal studies were included where foundational to established mechanistic understanding.

Studies were categorized into six thematic domains: genetic architecture and variant interpretation; mechanistic signaling pathways; fibrotic and remodeling biology; biomarker and multi-omics integration; therapeutic modality development; and reproducibility and translational risk. Within each domain, evidence was evaluated for mechanistic support strength, human validation, cross-cohort reproducibility, model fidelity, and therapeutic alignment. Rather than relying on citation frequency alone, emphasis was placed on mechanistic completeness and translational clarity. Publication bias was acknowledged as a limitation, given the likelihood that positive mechanistic findings are overrepresented in the published literature.

3. Mechanistic Architecture of Genetic Cardiomyopathies: From Sarcomere Dysfunction to Systems Remodeling

3.1. Sarcomeric Perturbation as the Initiating Event

HCM is most frequently caused by mutations in sarcomeric proteins that directly regulate actin-myosin cross-bridge kinetics. Variants in MYH7 alter ATPase cycling and force generation efficiency, while MYBPC3 mutations frequently result in haploinsufficiency or truncated proteins that destabilize thick filament regulation [9,10]. These structural perturbations translate into altered contractile energetics at multiple levels: increased cross-bridge duty ratio, enhanced calcium sensitivity, reduced energetic efficiency, and altered relaxation kinetics. Energetic inefficiency is particularly consequential, as increased ATP consumption relative to force output produces chronic energetic stress predisposing cardiomyocytes to metabolic remodeling.

In DCM, TTN truncations compromise sarcomeric elasticity and mechanosensing [2]. TTN's role extends well beyond structural scaffolding; it modulates mechanotransduction pathways influencing gene expression and remodeling programs. Both HCM and DCM thus converge on altered biomechanical signaling despite divergent phenotypic expression, a convergence with implications for both shared and distinct therapeutic targets.

3.2. Calcium Handling and Downstream Signaling Cascades

Altered sarcomeric function propagates into dysregulated calcium homeostasis. Increased myofilament calcium sensitivity in HCM may prolong calcium binding, impairing diastolic relaxation and activating calcium-dependent signaling pathways. One central pathway involves calcineurin-mediated dephosphorylation of NFAT transcription factors [11]. Activated NFAT translocates to the nucleus and induces hypertrophic gene expression programs. While extensively characterized in animal models, its quantitative contribution in human cohorts remains variable.

Calcium-dependent signaling intersects with MAPK cascades, PI3K-AKT pathways, reactive oxygen species generation, and mitochondrial stress responses. These interactions form a network rather than a linear chain. The translational implication is that targeting a single node may yield variable results depending on the network state, which itself is influenced by disease stage, genetic background, and comorbidities.

 doi:10.20944/preprints202603.2164.v1

3.3. Fibrosis and Extracellular Matrix Remodeling

Myocardial fibrosis emerges early in HCM and contributes to ventricular stiffness, arrhythmogenic substrate formation, and adverse clinical outcomes [12]. Fibrosis is driven by paracrine signaling between stressed cardiomyocytes and fibroblasts, mediated by TGF-ß activation, mechanical stress signals, and inflammatory mediators. However, fibrosis exhibits substantial heterogeneity: interstitial versus replacement fibrosis, regional variability, stage dependence, and significant influence of comorbidities such as hypertension and diabetes. Circulating fibrosis markers such as galectin-3 and Suppression of Tumorigenicity 2 (ST2) may reflect global remodeling rather than mutation-specific mechanisms [5], making fibrosis better suited as a progression marker than a mutation-specific therapeutic target.

3.4. Metabolic Remodeling and Energetic Stress

Energetic inefficiency is increasingly recognized as central rather than peripheral to cardiomyopathy pathogenesis. Sarcomeric hypercontractility increases ATP demand while mitochondrial dysfunction impairs supply. Metabolomic studies have revealed altered fatty acid oxidation, glycolytic flux, and redox balance in both HCM and DCM [5]. These metabolic shifts may precede overt hypertrophy, suggesting energetic stress is a proximal rather than secondary disease driver. However, metabolic signatures vary substantially across patient cohorts, influenced by age, diet, comorbid metabolic syndrome, and pharmacotherapy. This context dependence introduces translational risk: a metabolic target validated in one cohort may not generalize across populations with different metabolic backgrounds.

3.5. Inflammation, Immune Crosstalk, and Exosomal Signaling

Recent multi-omics analyses have identified inflammatory and immune-related pathways in subsets of cardiomyopathy patients [6]. Cytokine signaling, macrophage infiltration, and exosomal intercellular communication contribute to remodeling dynamics. Exosomal cargo profiles offer mechanistic insight but are highly sensitive to pre-analytic variation, including sample handling conditions, isolation protocols, and batch effects [7]. Immune pathway targeting may be appropriate for specific phenotypic subsets but is unlikely to be universally applicable across genetically defined cardiomyopathies, reinforcing the need for phenotypic stratification and concordance validation before broad therapeutic positioning.

Table 1. Comparative Translational Profiles of HCM and DCM.

Domain	HCM	DCM
Primary genetic drivers	MYH7, MYBPC3 (sarcomeric; gain-of-function / haploinsufficiency)	TTN truncations; also LMNA, SCN5A, RBM20
Proximal functional defect	Hypercontractility; increased cross-bridge duty ratio; enhanced Ca2+ sensitivity	Impaired force generation; cytoskeletal instability; mechanosensing failure
Mechanistic chain clarity	High — mutation to hypercontractility to obstruction relatively direct	Moderate-Low — broader multi-pathway remodeling cascade
Penetrance	Variable; strongly modulated by common genetic variants and lifestyle factors [4]	Incomplete; environmental triggers (myocarditis, pregnancy) play a major role [13]

 doi:10.20944/preprints202603.2164.v1

Fibrosis profile	Interstitial and replacement; can appear early; regionally variable [12]	Progressive dilation-associated; late-stage dominant
Molecular stability (pathway level)	Higher for proximal sarcomeric targets; lower for downstream remodeling	Generally lower; context-dependent pathway activation across cohorts
Therapeutic success example	Mavacamten (EXPLORER-HCM, 3); targets hypercontractility directly	No equivalent proximal target; neurohormonal agents standard; gene therapy investigational
Preferred translational strategy	Upstream sarcomere modulation; phenotype-proximal targeting	Systems-level stabilization; remodeling control; multi-target approaches

Note. HCM = hypertrophic cardiomyopathy; DCM = dilated cardiomyopathy; Ca2+ = calcium. EXPLORER-HCM = [3]. Stability classifications reflect synthesis of evidence described in Sections 3–5.

4. Translational Challenges: Heterogeneity, Penetrance, Biomarker Instability, and Model Limitations

4.1. Genetic Heterogeneity and Incomplete Penetrance

HCM and DCM are frequently described as monogenic diseases. In practice, they are mechanistically heterogeneous disorders shaped by genetic background, environmental exposure, hemodynamic stress, and temporal remodeling dynamics. Harper et al. [4] demonstrated that common genetic variants and modifiable risk factors influence susceptibility and expressivity in HCM, reframing cardiomyopathy from a purely monogenic model to a genetically modulated disease spectrum. Even within families carrying identical primary sarcomeric variants, left ventricular wall thickness, fibrosis burden, and arrhythmic risk vary substantially.

DCM exhibits similar complexity. TTN truncations represent a major genetic contributor, but penetrance is incomplete and disease severity is variable. Environmental triggers such as viral myocarditis, pregnancy, and chronic hypertension interact with genetic predisposition to influence clinical presentation [13]. From a translational standpoint, incomplete penetrance creates a fundamental problem: molecular signatures derived from one cohort may reflect a subset of modifier interactions rather than universal disease biology, and therapeutic targets positioned in signaling cascades may carry context-dependent relevance that does not generalize.

4.2. Pathway Convergence and the Causal-Compensatory Distinction

Despite heterogeneity, certain mechanistic themes recur. Sarcomeric mutations alter cross-bridge cycling kinetics, ATP utilization, and calcium sensitivity [10], triggering secondary stress signaling through calcineurin-NFAT, MAPK pathways, and metabolic remodeling [11]. Over time, fibroblast activation and extracellular matrix expansion lead to myocardial fibrosis [12]. However, phenotypic convergence does not imply identical upstream drivers. In HCM, hypercontractility and energetic inefficiency dominate early pathophysiology. In DCM, impaired force generation and cytoskeletal instability are more central. In Lamin A/C-related cardiomyopathy, nuclear structural integrity and mechanotransduction play prominent roles.

Translational programs must therefore ask whether a pathway node is causal, compensatory, or epiphenomenal in a given disease stage and genotype context. A sarcomere-targeted therapy may benefit obstructive HCM but offer limited impact in fibrosis-dominant late-stage disease. Failure to make this causal-compensatory distinction is among the most common sources of late-stage development failure in cardiomyopathy programs.

 doi:10.20944/preprints202603.2164.v1

4.3. Biomarker Instability and Technical Variability

Traditional heart failure biomarkers such as BNP and N-terminal proBNP reflect hemodynamic stress and are clinically useful but mechanistically nonspecific. Multi-omics approaches have been proposed to refine diagnosis and stratification [5]. Novel biomarkers including ST2, galectin-3, microRNAs, and cell-free DNA are under investigation. Yet translation to routine practice remains limited due to technical variability, cost, and the need for large-scale validation.

Biomarker instability arises from pre-analytic variation in sample handling, platform-specific detection biases, population heterogeneity, and temporal changes in disease stage. Exosomal biomarkers exemplify these challenges; isolation methods, normalization strategies, and batch effects substantially influence measured cargo profiles [7]. Without standardized workflows, reproducibility across laboratories becomes unreliable. For development teams, biomarker instability has direct consequences: if a proposed pharmacodynamic marker shifts due to handling variability rather than biological modulation, dose-response interpretation becomes unreliable and enrichment strategies collapse in multicenter trials.

4.4. Model Limitations and Physiologic Mismatch

Preclinical models are indispensable yet imperfect. Rodent models differ from humans in heart rate, ion channel distribution, myosin isoform expression, and metabolic regulation. Murine hearts rely predominantly on alpha-myosin heavy chain, whereas human ventricles express predominantly beta-myosin heavy chain, influencing both contractile dynamics and drug responsiveness in ways that may not be apparent until clinical trials.

Human induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) offer patient-specific platforms but remain developmentally immature unless subjected to rigorous maturation protocols [14]. Immature electrophysiology and metabolic profiles can distort pathway activation patterns critical to cardiomyopathy biology. Furthermore, most in vitro systems lack the multicellular architecture of myocardium; fibroblasts, endothelial cells, and immune cells contribute significantly to remodeling dynamics that isolated cardiomyocytes cannot reproduce. Model selection must therefore be pathway-specific: a model is appropriate only if it reproduces the targeted mechanistic node and at least one downstream phenotype relevant to human disease.

The alpha- versus beta-myosin heavy chain mismatch between murine and human myocardium has had documented consequences in cardiac drug development. Rodent models express predominantly alpha-myosin heavy chain, which has a more rapid ATPase cycling rate and greater actin-sliding velocity than MYH7 which dominates the human adult ventricle. This difference is not merely quantitative—it fundamentally alters how sarcomeric modulators interact with the contractile apparatus. Early-generation cardiac myosin activators demonstrated robust positive inotropic effects in murine failure models that did not fully anticipate the dose-response relationships or contractile reserve dynamics observed in human clinical trials. The lesson is mechanistically precise: a drug that interacts with ATPase kinetics will behave differently in a system where the dominant isoform has a two- to threefold higher intrinsic cycling rate. Model selection must therefore match not only the pathway but the molecular isoform context. This isoform specificity consideration is captured in the C5 domain of the Molecular Concordance Scoring Matrix and should be documented explicitly in any model validation package.

5. Reproducibility, Molecular Stability, and Development Risk

5.1. Clinical Annotation Is Not Molecular Validation

A pathogenic classification in ClinVar indicates accumulated clinical and genetic evidence supporting disease association [15]. It does not guarantee that the gene's downstream molecular phenotype will manifest consistently across independent cohorts, tissue samples, disease stages, or environmental contexts. The assumption that clinical pathogenicity implies molecular stability has

 doi:10.20944/preprints202603.2164.v1

been implicitly embedded in many translational programs. When this assumption is not examined directly, it introduces development risk that is rarely quantified but frequently realized.

Sarcomeric genes such as MYH7 and MYBPC3 have strong genetic credibility in HCM [1,9]. TTN truncations are well established in DCM [2]. These associations are robust at the genetic level. However, the transcriptomic, proteomic, and signaling consequences of these variants are not always consistent across datasets. Cohort composition, disease stage, ventricular loading conditions, medication exposure, and comorbidities all shape molecular readouts. Even fibrosis shows temporal variability, appearing early in some individuals but varying in magnitude and spatial distribution across patients and disease duration [12]. This variability is not statistical noise; it reflects biological heterogeneity that must be explicitly characterized rather than explained away.

Harper et al. [4] demonstrated that common genetic variants and modifiable risk factors influence HCM expressivity, meaning that even within a shared primary sarcomeric mutation, the broader genetic and environmental background modulates phenotype. When downstream molecular signatures are compared across cohorts without accounting for this variability, instability is often misinterpreted as technical inconsistency rather than recognized as biological context dependence—a misclassification with significant implications for development strategy.

5.2. Molecular Concordance as a Translational Gate

Reproducibility across independent human datasets should therefore function as an explicit translational gate. Before advancing a pathway node into an Investigational New Drug (IND)-enabling program, its directionality and magnitude of perturbation should be assessed across multiple cohorts. A molecular concordance framework integrates three measurable components: directional agreement across cohorts, effect size similarity, and statistical reproducibility after correction for multiple testing. Baseline inter-individual variability must also be benchmarked. The GTEx Consortium [16] demonstrated that gene expression variability differs substantially across tissues and genes, with some cardiac genes exhibiting tight normal distributions and others varying widely across individuals. A pathway signal exceeding expected baseline variability carries greater translational weight than one falling within physiological dispersion.

Concordance is not binary but graded. A pathway node may show strong directionality but variable effect size. Another may demonstrate modest shifts with remarkable stability across datasets. Translational prioritization should reflect this nuance by treating concordance as a scored property rather than a threshold criterion. Section 8 operationalizes this through the five-domain Molecular Concordance Scoring Matrix presented in Table 2.

Table 2. Molecular Concordance Scoring Matrix: Five-Domain Assessment for Translational Target Prioritization.

Domain	High (Score = 2)	Moderate (Score = 1)	Low / Unstable (Score = 0)
C1: Directional agreement	Consistent direction in 3 or more independent human cohorts	Consistent in 2 cohorts; divergent in 1 or more	Inconsistent direction across 2 or more cohorts
C2: Effect size consistency	Coefficient of variation (CV) of effect sizes 30% or less across cohorts	CV 30-60%; notable cohort-specific variation	CV greater than 60%; or effect size near zero in 1 or more cohorts
C3: Baseline variability ratio	Disease signal exceeds 2x normal inter-individual SD (GTEx benchmark)	Disease signal 1-2x normal SD	Disease signal falls within normal SD range

 doi:10.20944/preprints202603.2164.v1

C4: Genetic anchoring	Direct variant-to-pathway link; ClinVar P/LP with functional evidence	Plausible mechanistic link; limited functional confirmation	Pathway association only; no direct genetic linkage
C5: Model recapitulation	Pathway node reproduced in 2 or more validated human-relevant systems	Reproduced in 1 system; partial phenotypic alignment	Animal model or immature iPSC only; no phenotypic alignment
TOTAL SCORE	**8-10: High stability — Advance**	**5-7: Moderate — Conditional advance with validation plan**	**0-4: Unstable — Do not advance without orthogonal validation**

Note. CV = coefficient of variation. SD = standard deviation. GTEx = Genotype-Tissue Expression Consortium. ClinVar P/LP = Pathogenic or Likely Pathogenic. iPSC = induced pluripotent stem cell. Each domain (C1-C5) scored 0, 1, or 2. Maximum score = 10. Interpretation: 8-10 = High concordance (advance); 5-7 = Moderate (conditional advance with validation plan); 0-4 = Unstable (do not advance without orthogonal validation).

5.3. Development Risk Categories

Drug development programs implicitly assume stability at several levels: that the target is causally upstream of disease phenotype; that modulating the target will shift downstream biology; that downstream biology can be measured reliably; and that measurable signals correlate with clinical improvement. Instability at any of these levels increases risk, yet instability is rarely quantified early in development.

Sarcomere modulation provides an instructive contrast. Small-molecule myosin inhibitors target contractile mechanics directly, bypassing some upstream transcriptional variability. The clinical efficacy of mavacamten in obstructive HCM [3] illustrates how a phenotype-proximal target can succeed even when upstream signaling cascades vary. The mechanism is tightly linked to hypercontractility, a relatively stable functional phenotype. Targets positioned further upstream in signaling cascades—calcineurin-NFAT or MAPK nodes—may exhibit pronounced context dependence [11]. Without cross-cohort validation, distinguishing causal from reactive signaling becomes difficult. Concordance assessment becomes in this context a mechanism of risk control, forcing early confrontation with heterogeneity rather than deferring instability to late-phase trials where the cost of failure is highest.

6. Multi-Omics Integration and Artificial Intelligence: Opportunity and Methodological Fragility

Multi-omics technologies enable comprehensive profiling of transcriptomic, proteomic, metabolomic, and lipidomic states [5]. Artificial intelligence-driven integration promises to identify druggable nodes across these layers [6]. However, high dimensionality substantially increases the risk of overfitting and dataset-specific artifact. Feature importance in AI models may be unstable across resampled datasets. Without external validation, apparent mechanistic hubs may reflect cohort-specific structure rather than universal disease drivers.

The trajectory of epigallocatechin gallate (EGCG) research in heart failure and cardio-oncology offers a substantive cautionary case study [17]. EGCG has demonstrated mechanistic activity across multiple pathways implicated in cardiac remodeling—including attenuation of TGFß-driven fibrosis, modulation of sarcomeric calcium sensitivity, suppression of inflammatory signaling, and mitochondrial protection—producing a compelling multi-target mechanistic profile in cell-based and rodent systems. This apparent mechanistic breadth, however, illustrates the core translational problem that this work addresses: when a compound or a therapeutic strategy is active across many pathways simultaneously, mechanistic specificity collapses. It becomes difficult to establish which

 doi:10.20944/preprints202603.2164.v1

mechanism drives any observable clinical effect, to design a reproducible pharmacodynamic biomarker that could anchor dose-response interpretation, or to predict which patient subgroups will respond based on pathway activity. Multi-target mechanistic plausibility, in the absence of demonstrated cross-cohort concordance for a dominant pathway node, provides insufficient grounding for translational advancement. The EGCG example thus reinforces the framework's central principle: mechanistic richness and biological coherence are not substitutes for demonstrated molecular stability across independent cohorts.

Pre-analytic variability represents a particularly underappreciated vulnerability in multi-omics biomarker discovery. Proteomic and exosomal analyses are sensitive to sample handling conditions, isolation protocols, batch effects, and normalization strategies [7]. These factors introduce variance independent of disease biology. When biomarker signatures are subtle relative to technical noise, reproducibility deteriorates. Standardization initiatives are therefore essential prerequisites for any therapeutic stratification strategy built on multi-omics data.

A frequently overlooked benchmark is normal biological variance. GTEx (Genotype-Tissue Expression) data demonstrate substantial inter-individual variability in cardiac gene expression [16]. Disease-associated perturbations must be interpreted relative to this baseline. A gene exhibiting moderate fold-change in a single cohort may fall within normal variance when examined across a healthy population. Without baseline benchmarking, molecular stability may be systematically overestimated, leading to advancement of targets that will not survive contact with biological diversity in broader clinical contexts.

Robust validation of multi-omics and AI-derived targets should include independent replication cohorts, bootstrapped stability analysis, sensitivity analysis with input perturbation, and transparent reporting of model architecture [6]. Algorithmic sophistication must not be permitted to mask biological fragility.

6.1. Bridging Cardiac and Cardiometabolic Oncologic Instability

The molecular instability challenges described in genetic cardiomyopathy find a compelling parallel in the emerging intersection of metabolic liver disease and cardiac oncology. Metabolic dysfunction-associated steatotic liver disease (MASLD) and its inflammatory sequela, metabolic dysfunction-associated steatohepatitis (MASH), represent an increasingly recognized cardiometabolic nexus. Hepatocellular carcinoma (HCC) arising in the MASLD-MASH continuum is driven by overlapping oncogenic and cardiometabolic pathways, including mitochondrial dysfunction, inflammatory cytokine signaling, lipotoxicity, and insulin resistance—molecular mechanisms shared with cardiomyopathic remodeling. The identification of mRNA and microRNA-based drivers of HCC within the MASLD-MASH context highlights the same fundamental reproducibility challenge: transcriptomic biomarkers identified in one cohort must be validated across independent datasets before serving as therapeutic targets or stratification tools.

This cross-disease instability problem is mechanistically grounded. The fetal gene programs reactivated in hypertrophic cardiomyocytes overlap partially with oncogenic transcriptional reprogramming. TGF-beta-driven fibrosis is a shared remodeling pathway in both myocardial fibrosis and hepatic stellate cell activation in MASH. The calcineurin-NFAT axis implicated in maladaptive cardiac hypertrophy has documented roles in oncogenic signaling contexts. These mechanistic overlaps suggest that molecular concordance frameworks developed for cardiac target validation may be directly applicable to cardiometabolic oncology programs, and that cardio-oncology as a translational discipline will benefit from adopting the same reproducibility gates proposed here for genetic cardiomyopathy development.

7. Comparative Translational Profiles: HCM vs. DCM

Although often grouped together under the umbrella of genetic cardiomyopathy, HCM and DCM exhibit distinct translational profiles with important implications for target selection and development strategy. These differences are systematically summarized in Table 1.

 doi:10.20944/preprints202603.2164.v1

HCM frequently involves gain-of-function or hypercontractile sarcomeric states [10]. The mechanistic chain from mutation to hypercontractility to outflow tract obstruction is relatively direct. This mechanistic clarity, combined with a relatively stable proximal phenotype, likely contributed to the therapeutic success of sarcomere inhibitors [3]. Fibrosis and arrhythmia remain important secondary complications, but the proximal mechanical defect provides a clear therapeutic anchor with favorable molecular stability properties.

DCM, by contrast, frequently reflects structural instability and progressive dilation driven by titin truncations impairing mechanosensing and cytoskeletal integrity [2,13]. Remodeling involves metabolic shifts, inflammatory responses, and neurohormonal activation across a broader mechanistic canvas. The causal chain is less phenotype-proximal, and therapeutic targets are more distributed across the signaling landscape and less stable across cohorts. These differences argue for disease-specific concordance evaluation rather than assuming shared translational logic between HCM and DCM development programs.

7.1. Worked Example: Applying the Framework to TTN-Truncation in DCM

Step 1 — Genetic Credibility (C4 anchor): TTN truncating variants are among the most robustly established genetic contributors to DCM, identified in approximately 25% of familial and 18% of sporadic cases [2]. Large-scale sequencing programs have effectively separated disease-associated truncations from benign population-frequency variants. C4 scores 2: direct ClinVar P/LP linkage with functional evidence.

Step 2 — Mechanistic Chain Specification: The causal sequence from TTN truncation to sarcomeric elasticity compromise to mechanosensing failure is mechanistically grounded. TTN's role in Z-disc organization, passive tension generation, and mechanotransduction signaling is well characterized. However, the chain becomes inferential at the transition from cytoskeletal instability to downstream inflammatory activation, neurohormonal engagement, and progressive chamber dilation. These secondary remodeling steps are not titin-specific; they represent a shared final common pathway activated by diverse upstream insults. A therapeutic targeting TTN-specific mechanosensing must therefore demonstrate that its mechanism of action operates upstream of this convergence, not within the shared remodeling cascade.

Step 3 — Cross-Cohort Molecular Concordance: This is where TTN-related DCM earns a moderate rather than high concordance profile. While the genetic signal is stable, the transcriptomic and proteomic consequences of TTN truncation vary substantially across cohorts. Incomplete penetrance means that mutation carriers may remain clinically silent for decades. Environmental triggers—viral myocarditis, sustained hemodynamic overload, pregnancy—interact with the genetic predisposition to determine disease expression [13]. Cohorts enriched for recently symptomatic patients will show different pathway activation profiles than those including preclinical carriers. Directional agreement across cohorts (C1) is moderate; effect size consistency (C2) is limited by this contextual variability; baseline variability ratio (C3) depends critically on disease stage and comorbidity burden. Composite concordance score: approximately 5 to 6 of 10 — conditional advance category.

Step 4 — Biomarker Alignment: Circulating titin fragments have been investigated as damage markers in DCM, but their pharmacodynamic utility—as indicators of target engagement for a TTN-directed therapeutic—remains incompletely characterized. Mechanical stretch-responsive biomarkers and Z-disc integrity markers represent candidate pharmacodynamic tools but require standardized assay development and cross-site reproducibility validation before serving as trial enrichment or response endpoints.

Step 5 — Model Fidelity: iPSC-derived cardiomyocytes carrying TTN truncations can replicate mechanosensing failure and reduced passive force generation [14]. However, the progressive dilation and fibrotic remodeling that characterize human TTN-related DCM require multicellular architecture—fibroblasts, endothelial cells, macrophages—that isolated cardiomyocyte systems cannot reproduce. C5 scores 1: single-system validation with partial phenotypic alignment.

 doi:10.20944/preprints202603.2164.v1

Confirmation in engineered cardiac tissue or organoid systems with multicellular composition is required before Step 5 can score 2.

Strategic Conclusion — Conditional Advance: The TTN-DCM concordance profile argues for a conditional advance strategy: progression is warranted given strong genetic credibility, but must be contingent on a prospective validation plan that includes RWE-based phenotypic stratification to identify the subpopulation with active pathway engagement, stage-specific enrollment criteria that control for the environmental trigger variability identified in Step 3, and biomarker qualification for at least one mechanistically anchored pharmacodynamic readout before phase II initiation. This approach applies the framework's core principle: genetic credibility establishes the starting point, but molecular concordance determines the conditions under which advancement is responsible.

8. A Structured Translational Framework for Genetic Cardiomyopathy Development

Target validation in cardiomyopathy often follows a familiar trajectory: variant identification, pathway implication, model-based confirmation, and therapeutic hypothesis generation. What is frequently absent is a structured evaluation of reproducibility, mechanistic completeness, and development risk before advancement into costly translational programs. The following seven-step framework addresses these gaps. Each step is summarized operationally in Table 3, with cross-cohort concordance assessment (Step 3) operationalized through the scoring matrix in Table 2.

Table 3. Seven-Step Translational Framework: Operational Summary.

Step	Gate	Key Question	Failure Mode Addressed
1	**Genetic Credibility**	Is the variant robustly linked to disease with functional evidence?	Pursuing variants of uncertain significance
2	**Mechanistic Chain**	Is the causal path from variant to clinical phenotype fully specified at each step?	Targeting epiphenomenal or compensatory nodes
3	**Cross-Cohort Concordance**	Does the pathway signal replicate consistently across independent human datasets? (apply Table 2 scoring)	Cohort-specific false positives; biological instability undetected
4	**Biomarker Alignment**	Are pharmacodynamic and stratification biomarkers mechanism-linked and reproducible across sites?	Unreliable dose-response interpretation; trial enrichment failure
5	**Model Fidelity**	Does the preclinical system recapitulate the human mechanistic node and at least one downstream phenotype?	Model-specific artifacts that fail to translate to humans
6	**Modality Feasibility**	Is the therapeutic platform appropriate given the stability and reversibility profile of the mechanism?	Irreversible genomic intervention on context-dependent target
7	**Go/No-Go Criteria**	Are quantitative advancement thresholds defined prospectively before data are examined?	Post-hoc rationalization of advancement despite insufficient concordance evidence

 doi:10.20944/preprints202603.2164.v1

Note. PD = pharmacodynamic. iPSC-CMs = induced pluripotent stem cell-derived cardiomyocytes. Each step corresponds to a specific translational failure mode identified in the genetic cardiomyopathy development literature.

Step 1: Establish Genetic Credibility

Confirm variant-disease association through robust genetic evidence, segregation analysis, population frequency assessment, and functional validation [1,15]. For DCM, TTN truncations provide a model of strong genetic linkage that separates benign from disease-associated variants [2]. Genetic credibility establishes the starting point but does not specify the therapeutic target or confirm downstream molecular stability.

Step 2: Specify the Mechanistic Chain

Map the causal pathway from variant to phenotype explicitly: Variant to Protein dysfunction to Cellular phenotype to Tissue remodeling to Clinical manifestation. Each link must be supported by evidence and be mechanistically plausible. Anchor this mapping in established mechanistic literature [9,11,18]. Identify where the chain becomes inferential and where compensatory mechanisms may obscure primary drivers.

Step 3: Assess Cross-Cohort Molecular Concordance

Evaluate whether the pathway node exhibits consistent perturbation across independent human datasets. Apply the Molecular Concordance Scoring Matrix (Table 2) to generate a scored assessment across five domains: directional agreement (C1), effect size consistency (C2), baseline variability ratio (C3), genetic anchoring (C4), and model recapitulation (C5). Each domain is scored 0 to 2, yielding a maximum total of 10 points. Targets scoring 8 to 10 demonstrate high stability warranting advancement. Scores of 5 to 7 indicate moderate concordance requiring a conditional validation plan. Scores below 5 indicate biological instability; these targets should not advance without orthogonal validation across additional independent datasets.

These thresholds are operationally binding within the framework: a score of 8 to 10 triggers an unconditional Advance decision, permitting progression to IND-enabling studies without additional concordance requirements. A score of 5 to 7 triggers a Conditional Advance, requiring a prospectively defined validation plan—specifying additional independent cohorts, standardized biomarker assays, or genotype-stratified analyses—before proceeding to phase II initiation. A score below 5 triggers a Do Not Advance decision; the target must be reassessed with orthogonal validation from independent human datasets before re-entry into the scoring process. These thresholds are conceptual rather than empirically calibrated against historical development outcomes; future validation against a curated dataset of cardiomyopathy development programs would permit data-driven threshold refinement.

The concordance score does not require sophisticated statistical infrastructure. It requires that development teams explicitly document the evidence for each domain before making advancement decisions. The act of scoring itself forces early confrontation with heterogeneity that would otherwise be deferred to late-phase trials. Incorporate baseline expression variability from healthy myocardium [16] as a benchmark for the C3 domain.

Step 4: Align Biomarker Strategy

Select pharmacodynamic and stratification biomarkers that reflect the mechanistic node. Demonstrate reproducibility across sites and analytic pipelines [5,7]. Validate that the biomarker responds to modulation of the target before investing in it as a pharmacodynamic readout. Novel biomarkers must demonstrate not only mechanistic linkage but also practical stability under real-world collection and processing conditions.

 doi:10.20944/preprints202603.2164.v1

Step 5: Validate in Fit-for-Purpose Models

Confirm that chosen preclinical systems replicate both the targeted mechanistic node and at least one downstream phenotype relevant to human disease [14]. Recognize and document model limitations, particularly regarding maturation state of iPSC-CMs and absence of multicellular architecture. Positive results in systems that do not capture the human mechanistic chain should be treated as exploratory rather than confirmatory.

Step 6: Evaluate Modality Feasibility

Assess delivery, durability, reversibility, immunogenicity, and off-target risk according to therapeutic platform [19]. Mechanistic stability directly informs modality selection. A stable, mutation-proximal loss-of-function mechanism may justify durable genomic correction. A context-dependent signaling cascade may be better addressed with reversible small-molecule modulation. Misalignment between mechanism stability and modality irreversibility amplifies development risk substantially.

Step 7: Define Quantitative Go/No-Go Criteria

Establish predefined quantitative thresholds for molecular concordance score, target engagement, biomarker reproducibility, and safety margins. This final step transforms mechanistic insight into actionable development criteria and replaces narrative persuasion with structured evaluation. Go/no-go criteria must be defined prospectively, before data are examined, to prevent post-hoc rationalization of advancement decisions.

9. Clinical Trial Enrichment and Regulatory Implications

Clinical trials in genetic cardiomyopathies face a fundamental paradox. The diseases are genetically defined, yet phenotypically heterogeneous. Carriers of identical sarcomeric mutations may exhibit divergent trajectories influenced by modifier genes, environmental exposures, and metabolic status [4]. This heterogeneity can dilute therapeutic signal. If a mechanistic node is active only in a subset of patients, enrolling an unstratified population risks systematically underestimating the true treatment effect—a problem particularly acute for therapies targeting downstream pathways such as fibrosis or inflammatory signaling that may be stage- or context-dependent [5,12].

Real-world evidence (RWE) and electronic health record (EHR)-derived datasets offer a complementary and underutilized dimension for concordance validation in genetic cardiomyopathy. While clinical trials provide mechanistic purity, RWE captures the biological heterogeneity of real patient populations—variable comorbidity burden, concomitant pharmacotherapy, metabolic status, and longitudinal disease trajectory. Machine learning-powered risk calculators built on EHR data can quantify the baseline frequency of adverse events, stratify patient subgroups by pathway-relevant biomarkers, and identify modifier interactions that single-cohort transcriptomic analyses miss. In the context of molecular concordance assessment, RWE-derived phenotypic stratification provides an orthogonal validation layer: if a therapeutic target exhibits concordant transcriptomic behavior across independent GEO datasets but the corresponding phenotypic endpoint does not show consistent signal in RWE cohorts, this discordance should function as a developmental caution flag rather than being attributed to trial design variability. Integrating RWE-based adverse event risk profiling into the concordance scoring framework at Step 3 strengthens the translational evidence package and aligns with regulatory expectations for multi-source validation in genetic disease programs [15].

The success of sarcomere modulation in obstructive HCM offers an instructive contrast. Hypercontractility is phenotype-proximal and consistently expressed in obstructive disease [3,10]. Enrichment based on obstruction and symptomatic status contributed to reliable signal detection in the EXPLORER-HCM trial. Future trials targeting less stable downstream nodes may require molecular concordance-based stratification, baseline biomarker thresholds indicating pathway activation, polygenic risk-informed subgroup analyses [4], and stage-specific enrollment criteria.

 doi:10.20944/preprints202603.2164.v1

Trial design must integrate stability assessment upstream of randomization, not after enrollment failures reveal it.

Regulatory agencies increasingly emphasize biomarker qualification and mechanism-based development pathways. For a biomarker to serve as an enrichment or pharmacodynamic tool, reproducibility across sites and analytic platforms is critical. Exosomal biomarkers exemplify the regulatory challenge: isolation protocols vary, normalization standards are evolving, and AI-driven classification may introduce hidden biases [7]. GTEx-derived baseline variability data provide an additional benchmarking tool [16], and demonstrating that a disease-associated signal exceeds normal inter-individual variance strengthens regulatory credibility. Different therapeutic modalities carry distinct regulatory burdens; mechanistic stability directly informs modality choice, and regulatory confidence is strengthened when genetic anchoring, cross-cohort concordance, biomarker reproducibility, and model human fidelity can all be affirmatively demonstrated [14,19].

10. Discussion

Genetic cardiomyopathies occupy a unique position in cardiovascular medicine. They are among the best-characterized inherited cardiac disorders at the genetic level, yet they continue to challenge translational execution. Decades of research have clarified the molecular architecture of sarcomeric dysfunction, cytoskeletal instability, calcium signaling, and maladaptive remodeling [1,10]. At the same time, the field has experienced selective breakthroughs—sarcomere modulation in obstructive HCM [3] being the clearest example—contrasted by stalled or inconsistent programs targeting upstream signaling pathways. We argue that the limiting factor is no longer gene discovery or pathway identification, but the absence of structured evaluation of molecular stability, cross-cohort reproducibility, and mechanistic alignment prior to clinical advancement.

10.1. The Novelty of This Framework

Literature pertaining to cardiomyopathy have addressed molecular mechanisms in considerable depth [10,18], catalogued novel biomarkers and multi-omics discoveries [5], and surveyed therapeutic modalities from small molecules to gene editing [19]. What has not been proposed in the existing literature is a framework that formally positions cross-cohort molecular concordance as a scored, development-ready gate—a structured criterion that must be satisfied before mechanistic plausibility is permitted to advance a target toward clinical programs. The seven-step framework and accompanying Molecular Concordance Scoring Matrix introduced here represent this contribution. They do not introduce new biology. They introduce discipline: the requirement that stability be assessed explicitly, scored quantitatively, and documented prospectively rather than assumed narratively. The reframing of concordance from a quality-control afterthought to a mandatory translational gate is the primary novel contribution of this perspective and is the element absent from existing framework proposals in the cardiomyopathy literature.

10.2. Stability as a Translational Variable

Mechanistic plausibility has historically served as the primary gate for therapeutic prioritization. Yet plausibility does not equate to stability, and stability is what determines whether a mechanism will withstand the biological diversity encountered in clinical trials. The traditional monogenic framing of HCM and DCM oversimplifies clinical reality. Common variants and modifiable risk factors significantly influence expressivity [4]. TTN truncations demonstrate incomplete penetrance and variable severity [2]. Therapeutic programs must consider background genetic architecture, stage-specific pathway activation, and gene-environment interactions. Failure to stratify by these dimensions risks diluting therapeutic signal in ways that obscure genuine drug effects and lead to false-negative trial conclusions.

 doi:10.20944/preprints202603.2164.v1

10.3. Multi-Omics and AI: Calibrating Enthusiasm with Rigor

Multi-omics integration has expanded the candidate target landscape dramatically. Proteomic, metabolomic, and circulating biomarker studies identify novel mechanistic nodes and refine disease phenotyping [5]. AI workflows promise integrative prioritization across high-dimensional datasets [6]. Yet these approaches introduce fragility. Feature selection can be cohort-specific. Exosomal cargo profiles are sensitive to isolation protocols and batch effects [7]. Without transparent validation and external replication, sophisticated analytic pipelines may produce impressive internal metrics while lacking generalizability. The concordance scoring framework provides a structured means of evaluating AI-derived targets against the same stability criteria applied to classical pathway targets, ensuring that algorithmic discovery is held to the same reproducibility standards as conventional mechanistic research.

10.4. Model Fidelity and Platform Alignment

Preclinical systems remain indispensable but imperfect. Species differences in contractile protein expression and electrophysiology complicate translation [10]. iPSC-derived cardiomyocytes offer human genetic context but require maturation to approximate adult physiology [14]. A mechanistically complete validation package must demonstrate alignment across human genetic evidence, human molecular datasets, fit-for-purpose models, and biomarkers intended for clinical use. Platform selection interacts critically with mechanism stability: small molecules offer reversibility and titration, while RNA-based therapies and gene editing introduce durability but increase regulatory and safety complexity [19]. Modality choice should be driven by mechanistic context rather than technological enthusiasm.

10.5. Limitations

Several limitations merit consideration. First, heterogeneity in published datasets restricts direct quantitative comparison across studies. Second, publication bias may overrepresent positive mechanistic findings, potentially inflating perceived target robustness. Third, emerging modalities such as genome editing and regenerative reprogramming are evolving rapidly, and long-term safety profiles remain incompletely characterized. Fourth, the concordance scoring thresholds proposed in Table 2 are conceptual rather than empirically calibrated; validation against development outcomes across cardiomyopathy programs would strengthen their utility and permit threshold refinement. Fifth, this work does not represent a meta-analysis and does not provide pooled quantitative estimates; heterogeneity in study design, tissue sources, analytic pipelines, and patient populations limits direct comparison across datasets. Nonetheless, structured validation remains preferable to implicit assumption, and these limitations do not undermine the core argument for concordance as a translational gate.

11. Conclusions

Genetic cardiomyopathies have transitioned from gene discovery to mechanism-driven therapeutic exploration. The next phase of development requires equal emphasis on reproducibility, molecular stability, and translational alignment. Clinical pathogenicity does not guarantee mechanistic robustness across populations. Multi-omics discovery does not ensure external validity. Preclinical success does not confirm human pathway fidelity.

By integrating genetic credibility, mechanistic chain specification, cross-cohort concordance assessment, biomarker stability evaluation, fit-for-purpose model validation, and modality feasibility into a structured seven-step framework—operationalized through the Molecular Concordance Scoring Matrix—translational programs can better distinguish durable targets from context-dependent signals. Stability should be treated as a property of mechanism. Concordance should function as a development gate. Alignment between biology and therapeutic platform should guide modality choice.

 doi:10.20944/preprints202603.2164.v1

Such discipline does not slow innovation. It directs innovation toward mechanisms most likely to succeed and away from contexts where biological heterogeneity will defeat even the most mechanistically sophisticated therapeutic strategies. The field of genetic cardiomyopathy has the genetic clarity and mechanistic depth to support this next stage. What is now needed is the translational rigor to realize it.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

Generative AI Disclosure: In accordance with 2026 cardiovascular journal submission requirements, the authors disclose that AI tools were used in the preparation of this manuscript solely for the purposes of language refinement, structural organization, and literature synthesis assistance. All scientific assessments, framework development, mechanistic interpretations, scoring matrix design, and data interpretation are the original work of the authors. The authors take full responsibility for the accuracy, integrity, and originality of all technical content. No AI system generated or fabricated any citation, clinical data, or quantitative result presented in this perspective. All references have been independently verified against primary sources.

References

1. Seidman CE, Seidman JG. Identifying sarcomere gene mutations in hypertrophic cardiomyopathy: a personal history. Circ Res. 2011;108(6):743-750. doi:10.1161/CIRCRESAHA.110.223834.
2. Herman DS, Lam L, Taylor MR, Wang L, Teekakirikul P, Christodoulou D, et al. Truncations of titin causing dilated cardiomyopathy. N Engl J Med. 2012;366(7):619-628. doi:10.1056/NEJMoa1110186.
3. Olivotto I, Oreziak A, Barriales-Villa R, Abraham TP, Masri A, Garcia-Pavia P, et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2020;396(10253):759-769. doi:10.1016/S0140-6736(20)31792-X.
4. Harper AR, Goel A, Grace C, Thomson KL, Petersen SE, Xu X, et al. Common genetic variants and modifiable risk factors underpin hypertrophic cardiomyopathy susceptibility and expressivity. Nat Genet. 2021;53(2):135-142. doi:10.1038/s41588-020-00764-0.
5. Bastos JM, Colaco B, Baptista R, Gavina C, Vitorino R. Innovations in heart failure management: The role of cutting-edge biomarkers and multi-omics integration. J Mol Cell Cardiol Plus. 2025 Mar 1;11:100290. doi:10.1016/j.jmccpl.2025.100290. PMID: 40129519; PMCID: PMC11930597.
6. Sabry Z, Arora HS, Chandrasekaran S, Wang Z. AI-driven drug discovery and repurposing using multi-omics for myocardial infarction and heart failure. Explor Med. 2025;6:1001340. doi:10.37349/emed.2025.1001340.
7. Dinc R, Ardic N. Artificial Intelligence for Exosomal Biomarker Discovery for Cardiovascular Diseases: Multi-Omics Integration, Reproducibility, and Translational Prospects. Cells. 2026 Feb 5;15(3):304. doi:10.3390/cells15030304. PMID: 41677667; PMCID: PMC12896558.
8. Maron BJ, Rowin EJ, Maron MS. Global Burden of Hypertrophic Cardiomyopathy. JACC Heart Fail. 2018 May;6(5):376-378. doi: 10.1016/j.jchf.2018.03.004.
9. Schlossarek S, Mearini G, Carrier L. Cardiac myosin-binding protein C in hypertrophic cardiomyopathy: mechanisms and therapeutic opportunities. J Mol Cell Cardiol. 2011;50(4):613-620. doi:10.1016/j.yjmcc.2011.01.014.
10. Spudich JA. Hypertrophic and dilated cardiomyopathy: four decades of basic research on muscle lead to potential therapeutic approaches to these devastating genetic diseases. Biophys J. 2014;106(6):1236-1249. doi:10.1016/j.bpj.2014.02.011.
11. Molkentin JD. Calcineurin-NFAT signaling regulates the cardiac hypertrophic response in coordination with the MAPKs. Cardiovasc Res. 2004;63(3):467-475. doi:10.1016/j.cardiores.2004.01.021.

 doi:10.20944/preprints202603.2164.v1

12. Ho CY, Lopez B, Coelho-Filho OR, Lakdawala NK, Cirino AL, Jarolim P, et al. Myocardial fibrosis as an early manifestation of hypertrophic cardiomyopathy. N Engl J Med. 2010;363(6):552-563. doi:10.1056/NEJMoa1002659.
13. McNally EM, Golbus JR, Puckelwartz MJ. Genetic mutations and mechanisms in dilated cardiomyopathy. J Clin Invest. 2013;123(1):19-26. doi:10.1172/JCI62862.
14. Yang X, Pabon L, Murry CE. Engineering adolescence: maturation of human pluripotent stem cell-derived cardiomyocytes. Circ Res. 2014;114(3):511-523. doi:10.1161/CIRCRESAHA.114.300558.
15. Landrum MJ, Lee JM, Benson M, Brown GR, Chao C, Chitipiralla S, et al. ClinVar: improving access to variant interpretations and supporting evidence. Nucleic Acids Res. 2018;46(D1):D1062-D1067. doi:10.1093/nar/gkx1153.
16. GTEx Consortium. The GTEx Consortium atlas of genetic regulatory effects across human tissues. Science. 2020;369(6509):1318-1330. doi:10.1126/science.aaz1776.
17. Ajaz F, Haddad J, Huda B, Yousuf M, Patnaik R, Bhurka F, Banerjee Y. Epigallocatechin Gallate as a Molecular Therapeutic in Heart Failure and Cardio-Oncology: Mechanistic Pathways and Translational Perspectives. Int J Mol Sci. 2025;26(21):10798. doi:10.3390/ijms262110798.
18. Ashrafian H, McKenna WJ, Watkins H. Disease pathways and novel therapeutic targets in hypertrophic cardiomyopathy. Circ Res. 2011;109(1):86-96. doi:10.1161/CIRCRESAHA.111.242974.
19. Ma H, Marti-Gutierrez N, Park SW, Wu J, Lee Y, Suzuki K, et al. Correction of a pathogenic gene mutation in human embryos. Nature. 2017;548(7668):413-419. doi:10.1038/nature23305.
20. Butzner M, ElHabr AK, Farajkhah K, Chhatwal J, Ayer T, Gebrehiwet P, Shreay S, Riello RJ 3rd, Desai NR, Owens AT, Abraham T, Masri A. Epidemiology of Hypertrophic Cardiomyopathy in the United States From 2016 to 2023. JACC Adv. 2026 Feb;5(2):102552. doi: 10.1016/j.jacadv.2025.102552.
21. Kittleson MD, Meurs KM, Harris SP. The genetic basis of hypertrophic cardiomyopathy in cats and humans. J Vet Cardiol. 2015;17(Suppl 1):S53-73. doi:10.1016/j.jvc.2015.03.001.
22. Wiethoff I, Sikking M, Evers S, Gabrio A, Henkens M, Michels M, Verdonschot J, Heymans S, Hiligsmann M. Quality of life and societal costs in patients with dilated cardiomyopathy. Eur Heart J Qual Care Clin Outcomes. 2024 Jun 20;10(4):334-344. doi: 10.1093/ehjqcco/qcad056.