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From Hypertrophy to Heart Failure: What's New in Genetic Cardiomyopathies

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Abstract

Purpose of Review—The purpose of this review is to provide an update on the recent advances in the research and clinical care of patients with the major phenotypes of inherited cardiomyopathies - hypertrophic, dilated, and arrhythmogenic. Developments in genetics, risk stratification, therapies, and disease modeling will be discussed.

Recent Findings—Diagnostic, prognostic, and therapeutic tools which incorporate genetic and genomic data are being steadily incorporated into the routine clinical care of patients with genetic cardiomyopathies. Human pluripotent stem cells are a breakthrough model system for the study of genetic variation associated with inherited cardiovascular disease.

Summary—Next generation sequencing technology and molecular-based diagnostics and therapeutics have emerged as valuable tools to improve the recognition and care of patients with hypertrophic, dilated, and arrhythmogenic cardiomyopathies. Improved adjudication of variant pathogenicity and management of genotype-positive/phenotype-negative individuals are imminent challenges in this realm of precision medicine.

Keywords

hypertrophic cardiomyopathy; dilated cardiomyopathy; arrhythmogenic right ventricular dysplasia; pluripotent stem cells; genetic testing; genomics

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Compliance with Ethics Guidelines

Human and Animal Rights: All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

INTRODUCTION

In 1961, John F. Goodwin designed a classification system for cardiomyopathy based on his personal observations of cardiac structural and functional changes in 66 patients. His tripartite taxonomy identified (1) cardiac dilatation, (2) constriction, and (3) inflow or outflow obstruction. This early insight was validated through modern imaging techniques and corresponds with three phenotypes we now recognize as dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), and hypertrophic cardiomyopathy (HCM), respectively [1]. A fourth form of cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), was identified later [2, 3]. Recognizing the familial segregation of these disorders facilitated our understanding of these cardiomyopathies as largely monogenic. Almost 60 years after Goodwin's initial observations about structure and function, we can now also classify these cardiomyopathies based on their genetic and molecular alterations [4, 5].

Human pluripotent stem cells (hPSCs) provide a unique model system for the study of genetic alterations associated with inherited cardiovascular disease (Figure 1). Among their advantages, they can be differentiated into any somatic cell type and can generate extremely large numbers of cell progeny. Induced pluripotent stem cells (iPSCs) are now the most widely used type of hPSCs and are produced by reprogramming human somatic cells with the heterologous expression of certain transcription factors [6]. For monogenic disorders, iPSCs are an exemplary disease modeling system because they are genetically matched to the person from whom they were derived without many of the epigenetic influences that might contribute to disease phenotype [7]. Studies performed with iPSCs that have been differentiated into cardiomyocytes (iPSC-CMs) have already proven successful in helping us understand the cellular consequences of mutations that lead to genetic cardiomyopathies [8].

Recent rapid growth in genetic and genomic technologies has also transformed the clinical care of patients with inherited cardiomyopathies. Within the last 15 years, available strategies for genetic testing have advanced from targeted multigene cardiomyopathy panels to more agnostic platforms, including whole exome and whole genome sequencing [9, 10]. Defining the genetic cause of cardiomyopathy through testing provides opportunities for disease screening and risk stratification for affected individuals and their family members [11]. As our techniques to identify individuals with genetic cardiomyopathy improve, our knowledge regarding the genetic architecture of these disorders must keep pace. Here we will review the latest bench-to-bedside developments in three major phenotypes of inherited cardiomyopathies with a focus on genetics, risk stratification, therapy, and disease modeling.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is characterized by increased left ventricular wall thickness unexplained by cardiac loading conditions and a nondilated LV with preserved or increased ejection fraction. A "phenotype-positive" individual is recognized by a maximal left ventricular wall thickness ≥ 15 millimeters with ≥ 13 millimeters considered borderline [12, 13]. Older echocardiography-based studies in diverse cohorts established the general population prevalence of HCM at 0.16–0.23% (~1 in 500) [14–19]. Enhanced phenotype detection with advanced diagnostic imaging, widely available commercial genetic testing,

protocolized clinical screening of family members, and larger genetic population studies offer evidence for a revised prevalence estimate of 1 in 200 [20].

Hypertrophic cardiomyopathy is largely considered to be a monogenic disorder with autosomal dominant inheritance caused by variants in genes that encode sarcomere proteins. Variants in two genes, beta-myosin heavy chain (*MYH7*) and myosin-binding protein 3 (*MYBPC3*), are responsible for disease in about 50% of individuals with familial HCM [21–24]. Less than 10% of cases can be attributed to seven other genes that encode sarcomere proteins: cardiac troponin T (*TNNT2*), cardiac troponin I (*TNNI3*), alpha-tropomyosin (*TPM1*), cardiac alpha-actin (ACTC1), regulatory myosin light chain (*MYL2*), essential myosin light chain (*MYL3*), and cysteine and glycine-rich protein 3 (*CSRP3*) [25–31]. In addition to variants in the genes above, other genetic and environmental factors with a range of effect sizes are believed to contribute to the variable penetrance and expression of HCM. At least 15 additional sarcomere and non-sarcomere genes have been implicated in HCM, however variants in these and other “missing causal genes” occur less frequently and in smaller families resulting in weaker evidence for causality [32, 33]. In ~40% of HCM cases, the causal genes remain unknown [34].

Individuals with HCM become symptomatic due to diastolic dysfunction, left ventricular outflow tract (LVOT) or intracavitary obstruction, myocardial oxygen supply-demand mismatch, and atrial and ventricular arrhythmias. Beta-adrenergic receptor blockers remain the mainstay of pharmacologic treatment and are used to decrease obstruction, increase diastolic duration, and reduce myocardial ischemia [35]. Disopyramide, in combination with beta-blockers, is used to alleviate obstructive symptoms and to the reduce LVOT gradient [36]. In patients who do not respond to or cannot tolerate beta-blockers, symptomatic benefit can be achieved with nondihydropyridine calcium channel blockers such as diltiazem and verapamil [37]. Septal reduction strategies (surgical septal myectomy and alcohol septal ablation) are reserved for patients with severe symptomatic LVOT obstruction despite maximally tolerated or optimal pharmacologic therapy. At experienced centers, surgical myectomy now has a <1% 30-day operative mortality with a majority of patients experiencing symptom relief [38–40]. Left ventricular assist device implantation has emerged as a mechanical support strategy for patients with end-stage HCM. In the largest published series of continuous flow left ventricular assist device therapy in HCM and restrictive cardiomyopathy (RCM), overall survival of HCM and RCM patients was similar to that of traditional dilated cardiomyopathy (DCM) patients. Survival was worse for those with a preimplant left ventricular end diastolic dimension of < 5.0 centimeters [41]. HCM patients comprise ~1% of heart-only transplant recipients in the United States, and their post-transplant survival is comparable to those with non-HCM diagnoses [42, 43].

Ventricular arrhythmias and sudden cardiac death (SCD) are the most feared complications of HCM. Accordingly, risk stratification algorithms aim to identify individuals at increased risk for SCD who would benefit from prophylactic implantable cardioverter defibrillator (ICD) implantation. The 2011 American College of Cardiology Foundation/American Heart Association HCM guidelines highlighted five conventional risk factors, drawing primarily from observational studies, for the estimation of SCD risk: (1) a family history of SCD; (2) maximal left ventricular wall thickness ≥ 30 millimeters; (3) unexplained syncope; (4)

nonsustained ventricular tachycardia; and (5) abnormal blood pressure response to exercise [12]. In a departure from the U.S. framework, the 2014 European Society of Cardiology guidelines added a Class I recommendation for the use of a new SCD risk prediction model – HCM Risk-SCD [13]. HCM Risk-SCD was derived from a retrospective, multi-center longitudinal cohort study of 3,675 consecutive patients with the goal to provide a 5-year individualized risk estimates of SCD. Variables in the model include age, severity of left ventricular hypertrophy, left atrium size, LVOT gradient, family history of SCD, nonsustained ventricular tachycardia, and unexplained syncope. HCM Risk-SCD was internally validated and improved risk prediction (c-statistic from 0.54 to 0.7) compared to a more traditional model using four major risk factors [44]. A few smaller external validation efforts have suggested that the HCM Risk-SCD model is superior to previous models, however the most recently published validation study found that it performed well at lower and higher levels of risk but less well at intermediate risk levels [45–49]. Late gadolinium enhancement on cardiac magnetic resonance imaging (CMR), another potential risk marker, has been shown to be associated with SCD but has not yet been incorporated into formal prediction models [50, 51]. The highly anticipated Hypertrophic Cardiomyopathy Registry, planned to conclude in 2022, aims to improve SCD prognostication with international prospective analyses of clinical, imaging, genetic, and biomarker data [52].

In addition to clinical and imaging data, incorporating genetics into SCD risk prediction has shown some correlation with clinical outcomes. In a cohort that spanned nearly 30 years, HCM phenotype-positive carriers of likely pathogenic or pathogenic sarcomeric and non-sarcomeric variants had increased risks of all-cause death, cardiovascular death, heart failure-related death, and SCD/aborted SCD [53]. Despite pathogenic sarcomere variants being associated with an increase in heart failure events, there was no difference in events between *MYH7* and *MYBPC3* carriers in another study [54]. Overall, genotype status has been correlated with long-term outcomes but it alone cannot predict patient-specific outcomes given the contribution of modifying genetic, epigenetic, and environmental factors.

Although it may seem logical to obtain as much genetic data as possible for incorporation into risk prediction, the method of acquisition is important. Expanded gene panel testing did not significantly increase the sensitivity of pathogenic variant detection over a smaller panel in a broad referral population [55]. Newer agnostic platforms have shown more promise. In a comparison of whole genome sequencing (WGS) to multipanel gene testing, WGS identified 19 of 20 variants called as pathogenic, likely pathogenic, or uncertain significance and provided one new diagnostic finding. However, WGS also identified more variants of uncertain significance and secondary genetic findings, emphasizing the importance of expertise in clinical genetics and genomics when translating WGS to clinical care [9]. In an Australian HCM cohort in which targeted panel testing had not previously identified causal variants, WGS found a pathogenic or likely pathogenic variant in 20% of families and identified plausible disease-causing intronic and mitochondrial variants [10]. These technologies may serve to expand the population of “genotype-positive/phenotype-negative” individuals.

To date, pharmacologic and interventional therapies for HCM have not targeted the underlying genetic defect or affected intermediary pathways. However, experimental disease-modifying and molecular therapies are under development. The VANISH (Valsartan for Attenuating Disease Evolution in Early Sarcomeric HCM) trial is a multicenter, double-blind, placebo-controlled, phase II, randomized clinical trial to assess the safety and efficacy of valsartan in attenuating HCM disease progression in unaffected or mildly affected sarcomeric variant carriers with New York Heart Association Class I-II symptoms [56]. Mavacamten is an oral small molecule that regulates cardiac myosin ATPase and was shown to prevent hypertrophy and reduce myocyte disarray and interstitial fibrosis in murine models [57]. The safety and efficacy of mavacamten in symptomatic obstructive HCM is being tested in PIONEER-HCM, a phase 2 open-label trial. Preliminary data show that mavacamten reduces post-exercise peak LVOT gradient, resting LVOT gradient, and subjective dyspnea scores while increasing peak exercise oxygen consumption [58]. Modeling with iPSC-CMs also demonstrate the potential to link sarcomere variant status with targeted pharmacologic therapy. Mutant iPSC-CMs generated from 10 affected and unaffected family members with an *MYH7* missense variant exhibited contractile arrhythmia and cellular enlargement in the setting of abnormal calcium handling. A similar phenotype was displayed by iPSC-CMs with a different *MYH7* missense variant. Both sets of these phenotypes could be normalized with verapamil treatment [59, 60]. Despite the preliminary nature of these results, it is evident that the genetic era of HCM is rapidly shifting focus to targeted therapeutics.

Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is characterized by ventricular enlargement with depressed myocardial contractility. This ventricular dysfunction often progresses to overt heart failure with reduced ejection fraction, making it the most common indication for adult heart transplantation worldwide [61]. Heart failure symptoms are the most frequent clinical manifestation of DCM, however it can also present with arrhythmia, SCD, and thromboembolic events. DCM is typically diagnosed by the detection of enlarged left ventricular dimension by echocardiography or cardiac magnetic resonance imaging. In first-degree relatives of individuals with newly diagnosed idiopathic DCM, left ventricular echocardiographic deformation parameters (strain, strain rate, fractional shortening) were significantly impaired compared to age- and sex-matched controls suggesting that familial DCM may be detectable prior to the development of left ventricular cavity enlargement [62].

Clinical trials have conventionally distinguished DCM patients on the basis of ischemic versus nonischemic idiopathic etiologies, with the latter comprising 30% to 40% of participants [63]. Recent meta-analyses suggest a 23% prevalence estimate of familial DCM, indicating an important genetic contribution to these nonischemic idiopathic DCM cases [64, 65]. Familial DCM has been defined by the presence of (1) > 2 affected relatives with DCM or (2) a relative of a DCM patient with unexplained sudden death before the age of 35 years, however these definitions have not been uniformly applied across studies [66, 67]. Cases of nonfamilial or sporadic DCM have also been shown to have genetic bases, although the frequency of this finding is unknown [68]. In addition, the phenotypes of DCM attributed to nongenetic causes, such as hypertension, valvular disease, and toxin exposure, may be

influenced by genetic and epigenetic factors. Overall, the true prevalence of genetically-mediated DCM remains undetermined due in part to this heterogeneity in classification.

A genetic cause of cardiomyopathy can be identified in 30% to 40% of patients with familial DCM [69]. The majority of these causes are inherited in an autosomal dominant fashion with variable penetrance and expressivity. The most commonly mutated gene in familial DCM is titin (*TTN*), followed by lamin-A/C (*LMNA*), myosin-7 and −6 (*MYH7* and *MYH6*), sodium channel protein type 5 subunit alpha (*SCN5A*), *MYBPC3*, and *TNNT2* [70]. Autosomal recessive, X-linked recessive, and mitochondrial inheritance patterns have also been described [71]. Variants in over 50 genes that regulate a broad diversity of cellular functions have been associated with familial DCM. These genes encode proteins required for myocardial force generation, force transmission, sarcomere integrity, cytoskeletal and nuclear architecture, electrolyte homeostasis, mitochondrial function, and transcription. Efforts to capture this locus and allelic heterogeneity has led to the expansion of targeted DCM testing panels offered by clinical diagnostic laboratories. The ensuing improvements in diagnostic sensitivity have been countered by a higher number of inconclusive results at a greater cost [72]. Genome sequencing is being investigated as an alternative to multigene panel sequencing and has shown high accuracy for variant detection along with the added capacity to interrogate noncoding regions of the genome [73, 74].

Despite these advances in genetic testing, there are only a few genotype-phenotype correlations that can be made in familial DCM. Truncating variants (nonsense, frameshift, splice site) in *TTN*, a massive sarcomeric protein, are believed to cause 20% to 25% of familial DCM [75, 76]. In an integrated analysis of *TTN* sequence, protein, transcriptional, and phenotypic data of more than 5,200 individuals, individuals with DCM associated with *TTN* truncating variants experienced worse left ventricular function, more sustained ventricular tachycardia, and poorer heart failure outcomes compared to individuals with DCM without *TTN* truncating variants [76]. However, *TTN* truncating variants have also been identified in control and general population reference datasets, although the prevalence is lower [75, 77]. There is also a high prevalence of *TTN* missense variants in individuals without DCM - 23 variants per individual on average in the Exome Sequencing Project [78]. The clinical significance of these variants remains unclear, but iPSC modeling has provided some mechanistic insight. iPSC-CMs generated from DCM patients with either *TTN* truncating or missense variants displayed deficits in contractile function and limited compensatory reserve mechanisms in response to mechanical and β-adrenergic stress [79]. These phenotypes were similarly reproduced in genome-edited wild-type iPSC-CMs into which *TTN* truncating variants had been introduced [79].

Pathogenic variants in *LMNA* are the second most common cause of inherited DCM, occurring in 5% to 8% [80, 81]. *LMNA* encodes 2 proteins, lamins A and C, which are involved in many cellular processes including nuclear to cytoplasmic transport, mechanosignaling, and gene expression regulation. iPSC-CMs with either a *LMNA* nonsense or missense mutation exhibited increased nuclear bleb formation, micronucleation, and apoptosis upon electrical stimulation [82]. Pathogenic *LMNA* variants are inherited in an autosomal dominant pattern and are predictive of poor arrhythmic and heart failure-related outcomes [83, 84]. The clinical signatures of LMNA-associated DCM include

dysrhythmias (sinus and atrioventricular nodal dysfunction, atrial fibrillation, ventricular tachycardia, ventricular fibrillation, SCD) and progressive left ventricular systolic dysfunction, often necessitating advanced therapies. Multiple studies have described the high rate of appropriate ICD therapies for ventricular arrhythmia in DCM patients with disease-causing *LMNA* variants who had borderline or normal left ventricular systolic function and did not meet otherwise traditional criteria for ICD implantation [85–87]. The role of prophylactic ICD implantation in mitigating SCD risk has been addressed in both European and U.S. consensus documents, and ICD implantation should be addressed especially when individuals undergo pacemaker implantation for LMNA-associated conduction disease [88, 89].

In addition to DCM, other multisystem diseases associated with *LMNA* mutations, also called laminopathies, include limb-girdle muscular dystrophies, Charcot-Marie-Tooth neuropathy, autosomal Emery-Dreifuss muscular dystrophy, and lipodystrophy syndromes (e.g. Hutchinson- Gilford progeria syndrome).

While mutations in other genes such as *SCN5A*, filamin C (*FLNC*), and phospholamban (*PLN*) have been associated with high-risk features in DCM, the wide genetic heterogeneity and variable penetrance and expressivity has limited further translation to clinical management [90–92]. A number of studies have more specifically characterized the cellular and molecular consequences of mutations in DCM-associated genes with iPSC modeling (Table 1). The most intensively studied familial DCM iPSC lines to date were derived from a family whose affected members harbor a missense R173W variant in *TNNT2*. Compared to control line iPSCs generated from unaffected family members, the mutant iPSC-CMs exhibited abnormal calcium handling, reduced contractility, and myofibrillar disarray, which were exacerbated with β-adrenergic stimulation [93]. Other studies have demonstrated the potential of genome editing for phenotype correction; corrected iPSC-CMs showed reversal of calcium handling abnormalities caused by an in-frame deletion variant in *PLN* [94].

Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

Histopathologically, ARVC/D is characterized by the replacement of right ventricular myocardium by fibrous and fatty tissue. This fibrofatty infiltration predominantly involves the right ventricular (RV) free wall leading to thinning and aneurysmal enlargement [3, 95]. Inflammatory lymphocytic and histiocytic infiltrates, focal necrosis, and apoptosis have been observed in biopsy specimens, prompting investigation into the nebulous relationship between myocarditis and ARVC/D [96, 97]. The classical clinical phenotypes of RV precordial T-wave inversions, recurrent ventricular arrhythmia, and RV enlargement and failure first described in 1982 still comprise the basis for the updated international task force criteria used to diagnose ARVC/D [3, 98]. Common but alarming clinical presentations include exercise-induced syncope and SCD. Available therapies aim to reduce SCD risk and alleviate heart failure and arrhythmic symptoms. Left ventricular involvement, manifested by inferior and/or lateral T-wave inversions, ventricular arrhythmias with right bundle branch block morphology, and pump dysfunction, has been described as a distinct pattern of disease expression, leading some to suggest a nomenclature revision to “arrhythmogenic cardiomyopathy” [99]. Similar to other genetic cardiomyopathies, pathologic,

electrocardiographic, echocardiographic, and MRI phenotypes are used to make the diagnosis. However, ARVC/D is the only cardiomyopathy in which the presence of a known pathogenic variant is currently incorporated into the diagnostic framework [98].

Most often, causal genes in ARVC/D cases encode the desmosomal proteins plakophilin-2 (*PKP2*), desmoplakin (*DSP*), desmoglein-2 (*DSG2*), desmocollin-2 (*DSC2*), and junction plakoglobin (*JUP*) which are critical to intercellular adhesion, signal transduction, and maintenance of tissue integrity [100–104]. Variants in these genes are typically inherited in an autosomal dominant pattern with incomplete penetrance and variable expression and have been identified in 33% to 63% of probands [105]. The estimated overall rate of successful genetic screening in individuals who meet international task force diagnostic criteria is 50% [106]. In multiple cohorts, only 30% to 40% of at-risk relatives carrying identified desmosomal variants fulfill diagnostic task force criteria [107, 108]. Sex-related hypotheses for this variable penetrance are based on observations of lower disease expressivity in women carrying desmosomal gene mutations and more malignant outcomes, including SCD, in men [109, 110]. Sex differences in reproductive hormones and in rates of participation in endurance athletics, a risk factor for early manifestation and progression of disease, have been proposed as reasons for this discrepancy [111]. Digenic inheritance and compound heterozygosity are frequent and can manifest with more severe phenotypes, further complicating the narrative of simple monogenic inheritance [112]. These issues with genetic diagnosis along with the need for advanced imaging and electrophysiologic evaluation (i.e. CMR, signal-averaged electrocardiogram, electroanatomic mapping) required to diagnose ARVC/D likely contribute to underestimation of familial disease.

Non-desmosomal genes including *CTNNA3* (alpha T-catenin), *CDH2* (N-cadherin), *TMEM43* (transmembrane protein 43), *LMNA*, *TTN*, *PLN*, *RYR2* (ryanodine-receptor type 2), and *SCN5A* have been associated with ARVC/D, although with different electrical phenotypes [105]. Similar to HCM and DCM, the expansion of WES and WGS into genetic evaluation for ARVC/D has raised issues regarding the interpretation of rare desmosomal and non-desmosomal variants and of variants of unknown significance. Classification of desmosomal missense variants has been particularly problematic with some *PKP2* variants being reclassified after initially being thought to be pathogenic [105]. Segregation studies to inform pathogenicity are limited in ARVC/D by small family sizes and incomplete penetrance. Five genes implicated in ARVC/D pathogenesis (*PKP2*, *DSP*, *DSG2*, *DSC2*, *TMEM43*) are included in the American College of Medical Genetics and Genomics list of 59 medically actionable genes recommended for return of results in clinical genomic sequencing [113]. While this genome-first approach could provide an early opportunity for disease prevention, the lack of evidence regarding the appropriate diagnostic evaluation, risk stratification, lifestyle modification, and follow-up for these presumed genotype- positive/ phenotype-negative individuals should be addressed.

iPSC modeling for ARVC/D has mirrored the complexities of eliciting disease phenotypes in humans. The most intensively studied ARVC iPSC lines to date were derived from two unrelated individuals, one homozygous for a *PKP2* variant that causes a splicing defect and the other heterozygous for a *PKP2* frameshift variant [114]. The iPSC-CMs from these individuals manifested ARVC-related phenotypes only when they were treated with five

adipogenic factors which led to increased lipogenesis and apoptosis and abnormal calcium handling. In another study, iPSC-CMs from two patients heterozygous for different *PKP2* frameshift variants had increased lipid accumulation and desmosomal disruption in standard differentiation conditions, and these phenotypes became exaggerated with treatment with adipogenic factors [115]. Similar findings were observed in another study with iPSC-CMs from an individual heterozygous for a *PKP2* missense mutation [116]. While certainly provocative, extrapolation of these findings to causality for disease development in native human myocardium is still premature.

CONCLUSION

Classification of the genetic cardiomyopathies has long relied upon pattern recognition of cardiac structure and function. Rapid progress in next generation sequencing technology, bioinformatics, and functional genomics has facilitated the personalization of diagnosis and management for individuals with hypertrophic, dilated, and arrhythmogenic cardiomyopathy. These tools are becoming more widely available and less expensive and hold great potential for mechanistic insight into inherited cardiovascular disorders. Standardizing and centralizing clinically relevant genomic knowledge will be imperative for accurate variant annotation, precise risk stratification, and achievement of optimal outcomes.

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Conflict of Interest

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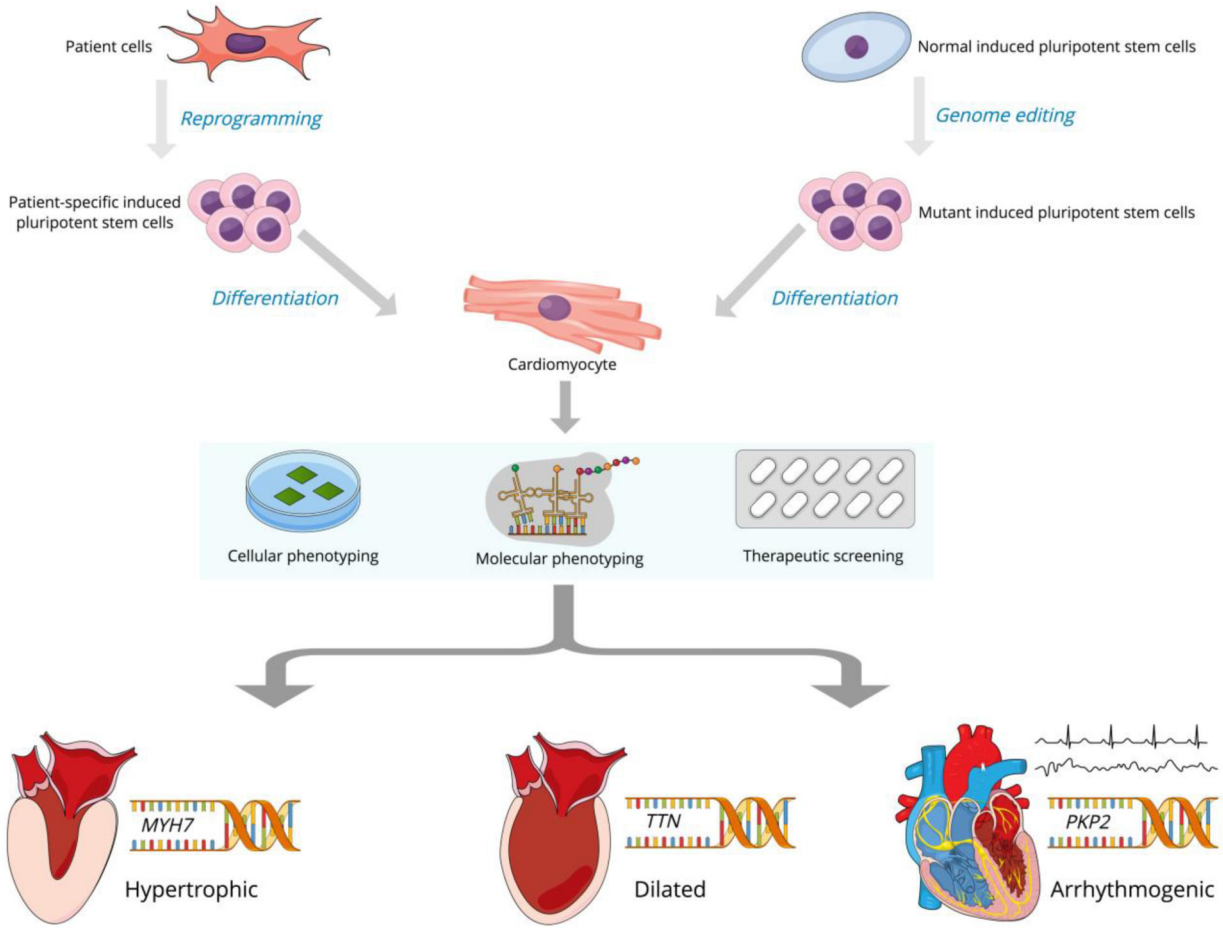

Figure 1.
Human pluripotent stem cells for modeling of genetic cardiomyopathies

Table 1

Cardiomyopathies modeled with human pluripotent stem cell cells

Disease modeled	Mutated gene	Type of variant	Reference
Dilated cardiomyopathy	*TTN*	Truncating, Missense	[79]
	TNNT2	Missense	[93]
	LMNA		
	PLN	In-frame deletion	[94]
	DES	Missense	[117]
Hypertrophic cardiomyopathy	*MYH7*	Missense	[59, 60]
Arrhythmogenic right ventricular cardiomyopathy/dysplasia	*PKP2*	Splicing defect, Frameshift, Missense	[114–116]
Duchenne muscular dystrophy	*DMD*	Frameshift, Nonsense	[118, 119]
Barth syndrome	*TAZ*	Frameshift, Missense	[120]
Left ventricular noncompaction	*TBX20*	Nonsense	[121]
	GATA4	Missense	[122]
Restrictive cardiomyopathy	*FLNC*	Missense	[123]

TTN, titin; TNNT2, cardiac troponin T; LMNA, lamin A/C; PLN, phospholamban; DES, desmin; MYH7, beta-myosin heavy chain; PKP2, plakophilin 2; DMD, dystrophin; TAZ, tafazzin; TBX20, T-box 20; GATA4, GATA binding protein 4; FLNC, filamin C