Review Article

Narrative review of pediatric heart failure in the age of precision medicine

Nishma Valikodath[1], Justin Godown[2]^, Aryaz Sheybani[3]

[1]Department of Pediatrics, Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, TN, USA; [2]Division of Pediatric Cardiology, Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, TN, USA; [3]Nemours Cardiac Center, Nemours Children's Hospital, Wilmington, DE, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Justin Godown. Division of Pediatric Cardiology, Monroe Carell Jr. Children's Hospital, 2200 Children's Way, Doctor's Office Tower Suite 5230, Nashville, TN 37232, USA. Email: justin.godown@vumc.org.

Background and Objective: Improvement in the affordability and convenience of genetic testing has rapidly expanded the understanding of the mechanistic causes of various pediatric cardiomyopathies. Concurrently, new therapies are being developed to better-target specific pathologies as opposed to classic therapies that treat the maladaptive processes of chronic heart failure. This review will discuss the advances in genetic testing and specific therapies that have been shown to benefit or potentially benefit genetically distinct subsets of the pediatric population with heart failure or at risk of developing heart failure.

Methods: We undertook a comprehensive database search (January 2000–August 2022) of PubMed, utilizing terms 'pediatric', 'cardiomyopathy', 'heart failure', 'genetics', and 'precision medicine'. Additional notable studies were obtained from ClinicalTrials.gov. Studies published in English that examine genetic basis and treatment modalities of pediatric heart failure.

Key Content and Findings: New and investigational therapies for hypertrophic cardiomyopathies associated with obstruction or Noonan syndrome, Fabry cardiomyopathy, Barth syndrome, Duchenne muscular dystrophy, single ventricle failure, and heart failure in specific demographics are discussed.

Conclusions: The rapid expansion of the genetic understanding of cardiomyopathy and heart failure as well as tailored therapies to specific molecular causes holds great promise for the future of pediatric heart failure treatment. Whereas conventional heart failure therapies target the maladaptive remodeling response that leads to worsening of heart failure, these therapies target the molecular causes of cardiomyopathy and heart failure in certain populations allowing for a potential to more significantly impact the clinical trajectory of pediatric heart failure.

Keywords: Heart failure; pediatric; precision medicine

Submitted Aug 31, 2022. Accepted for publication Feb 06, 2023. Published online Feb 16, 2023.
doi: 10.21037/tp-22-431
View this article at: https://dx.doi.org/10.21037/tp-22-431

Introduction

The landscape of therapies available in heart failure management has been rapidly expanding within the past decade. The American Heart Association (AHA) heart failure guidelines in 2013 only recommended medical therapy with angiotensin converting enzyme inhibitors (ACE-i) or angiotensin receptor blockers (ARB), beta blockers, mineralocorticoid receptor antagonists (MRA),

^ ORCID: 0000-0002-7068-0625.

Table 1 Search strategy summary

Items	Specification
Date of search	August 12, 2022
Databases and other sources searched	PubMed, Clinical Trials.gov
Search terms used	"pediatric", "cardiomyopathy", "heart failure", "genetics", "precision medicine"
Timeframe	January 2000–August 2022
Inclusion and exclusion criteria	Language: English
Selection process	Nishma Valikodath and Aryaz Sheybani conducted the selection by consensus

and in select populations, hydralazine and isosorbide dinitrate (ISDN) combination (1). Development of new therapies has been accelerating with multiple new classes of medications [ARB-neprilysin inhibitors (ARNi), soluble guanylate cyclase (sGC) stimulators, sodium-glucose cotransporter-2 inhibitors (SGLT2i) and I_f current inhibitors] becoming available and recommended for heart failure management most recently (2). Unfortunately, many of these recommendations for newer medications are based on data from studies in adult populations with cardiomyopathy. Pediatric studies are lacking and often adult data is extrapolated to the pediatric population due to insufficient data (3). Heart failure in pediatrics can generally be considered as a progressive syndrome with varying causes, including congenital heart malformations and genetic abnormalities, leading to cardiac dysfunction resulting in classical signs and symptoms (3).

The advent of rapid whole genome sequencing and identification of genetic etiologies of multiple pathologies has turned a focus on the possibilities of precision medicine. Pediatric patients with cardiomyopathy comprise a heterogeneous population with many different genetic loci that may present similar phenotypes through distinct mechanisms. As costs for whole genome sequencing have decreased (4), the potential for more widespread identification of genetic anomalies has increased as has the possibility of tailoring therapy to impact specific subpopulations. The National Research Council described the goal of precision medicine as "the selection of a subset of patients, with a common biological basis of disease, who are most likely to benefit from a drug or other treatment (5)". This review focuses on some of these advances in this developing field of medicine. We present the following article in accordance with the Narrative Review reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-22-431/rc).

Methods

A literature search of PubMed utilizing the terms 'pediatric', 'cardiomyopathy', 'heart failure', revealed 1073 results. When the search was narrowed to the last 22 years (January 2000–August 2022) published in the English language, 993 records were obtained. Of these results, studies pertaining to the genetic basis and treatment modalities of pediatric heart failure were examined. Adding "genetics" and "precision medicine" to our search strategy further narrowed the search to 8 results. Additional notable studies were obtained from ClinicalTrials.gov. Our search strategy is summarized in *Table 1*.

Pathophysiology of chronic heart failure (CHF) in the general population

Systolic heart failure stems from inadequate cardiac output. The body compensates to maintain cardiac output by either increasing stroke volume or increasing heart rate (6). These mechanisms are achieved primarily through activation of the sympathetic nervous system (SNS) and activation of the renin-angiotensin-aldosterone system (RAAS). The SNS releases catecholamines that increase systemic vascular resistance and heart rate, resulting in increased mean arterial pressure and increased organ perfusion. Activation of RAAS leads to increased angiotensin II and aldosterone release resulting in increased vasoconstriction and increased water retention.

These compensatory mechanisms exacerbate heart failure as well through adverse cardiac remodeling. Increased catecholamine levels lead to hyperactivity of the SNS, enhancing apoptotic pathways and resulting in cardiomyocyte death. Chronic catecholamine exposure can cause interstitial fibrosis and induce pump dysfunction through left ventricular (LV) dilation (7). Angiotensin

Table 2 Genetic syndromes, cardiac phenotypes, and disease-specific therapies

Syndrome	Genetic mutation	Phenotype	Disease-specific therapy
Noonan syndrome	RAS/MAPK signaling pathway (*PTPN11, SOS1, RAF1, KRAS, NRAS, RIT1*)	HCM	MEK-inhibitors (trametinib)
Fabry disease	Galactosidase A (GLA) gene	HCM	Migalast
Barth syndrome	*TAZ* gene	DCM, HCM, LVNC	Elamipretide
Duchenne muscular dystrophy	Dystrophin	DCM	Eteplirsen, Ataluren
Laminopathies	*LMNA* gene	DCM	ARRY-371797 (phase III)

HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; LVNC, left ventricular non-compaction; MAPK, mitogen-activated protein kinase.

II leads to fibroblast activation within cardiomyocytes, myocardial scarring, among other changes that involve complex cascades of signaling molecules (8). Atrial natriuretic peptide and B-type natriuretic peptide (BNP) which have a role in regulation of extracellular volume, natriuresis and diuresis, also inhibit renin secretion of aldosterone production. Their levels are increased in patients with CHF. These molecules also inhibit cardiac remodeling, apoptosis, and fibrosis (9,10). However, these mechanisms do not prevent or stop the development of heart failure as they are easily cleared by neprilysin, levels of which are increased in CHF (11,12). These have been the primary targets of traditional heart failure therapy that are the first line therapies for patient with progressive heart failure regardless of the molecular cause of heart failure (2).

Genetic basis of disease

The identified genetic causes of cardiomyopathy are known to have varying penetrance and variable expressivity within a population. Many pathogenic mutations have been identified to have different phenotypic expressions of disease (13). As more genes have been identified, genetic testing yielding positive results for pathogenic mutations have been increasing. These diagnostic yields can potentially be further increased by also incorporating genetic testing for genes known to cause heritable arrhythmias with cardiomyopathy testing (14). *Table 2* summarizes certain genetic syndromes with associated cardiomyopathies, and gene-targeted therapies.

Hypertrophic cardiomyopathy (HCM)

HCM is largely caused by mutations in sarcomeric proteins with autosomal dominant inheritance. While these genes have been well defined, yield of genetic testing in adult populations has been decreasing as less phenotypically severe disease is being diagnosed in the recent era. Identification of a causative mutation had been nearly 60% in the early era, that yield has fallen to under 40% more recently with the detection of more benign disease (15). A recent study in pediatric HCM reported sarcomeric variants in 63% of the HCM population when patients with non-sarcomeric variants are excluded, suggesting the yield of genetic testing in pediatrics remains quite robust (16). Non-sarcomeric causes of HCM [e.g., RASopathies, lysosome-associated membrane protein-2 (LAMP2), and α-galactosidase] comprise a proportion of the pediatric HCM and can be detected by genetic testing as well (17).

Dilated cardiomyopathy (DCM)

DCM is more genetically heterogenous with primarily autosomal dominant inheritance and over 100 genes that may have variants presenting with a DCM phenotype (18). Where the genes associated with development of HCM are most commonly sarcomeric, genes associated with DCM encode proteins for various functions including sarcomeric, cytoskeletal, mitochondrial, and desmosomal proteins (18). A pathogenic gene variation can be found in nearly 50% of patients with familial DCM (19). Studies of DCM may not include patients with neuromuscular syndromes [e.g., Duchenne muscular dystrophy (DMD)] known to develop a DCM phenotype, though they comprise 26% of the pediatric DCM population as the clinical pathology and progression appear to be distinct (20).

Restrictive cardiomyopathy (RCM)

RCM can be inherited or acquired. As it is a less common

form of cardiomyopathy, there have been fewer studies into the genetic etiology of RCM. Two studies with small sample sizes have described an association with variants in sarcomeric proteins that can present with an HCM phenotype (21,22). A pathogenic mutation was detected in as many as 60% of patients with RCM in one cohort (22). Other inherited causes of RCM include many of the storage diseases [e.g., glycogen storage disease, Fabry disease (FD), Gaucher disease, Hurler syndrome, Hunter syndrome, and Niemann Pick disease].

Single ventricle disease

While the phenotypes that comprise single ventricle heart disease are diverse, outcomes are universally poorer in patients with a hypoplastic or inadequate left ventricle (23). Our understanding of the molecular basis for development of single ventricular disease continues to develop, one pathway is due to primary ventricular hypoplasia (24). This has been demonstrated in a murine model of hypoplastic left heart syndrome (HLHS) where mutations of genes related to cardiomyocyte proliferation (*Sap130*) and epithelial to mesenchymal transition (*Pcdha9*) produced a functional phenotype with the features of HLHS (25).

Precision medicine prescriptions

Sarcomeric HCM

HCM often results in significant left-ventricular outflow tract (LVOT) obstruction leading to inadequate cardiac output and exertional intolerance. In 2006, a study reported 70% of patient with HCM having some level of obstruction (26), though this prevalence may be reduced with the recognition of more benign disease in the current era. As the disease progresses, patients can develop diastolic heart failure due to myocardial ischemia, myocyte disarray and progressive interstitial fibrosis. The traditional therapy for symptomatic HCM with LVOT obstruction when medical management fails has been septal reduction therapy to relieve the obstruction and allow for cardiac remodeling to improve systolic and diastolic function.

Data from mice showing losartan therapy prevented development of hypertrophy (27), prompting a study of valsartan in pediatric patients with sarcomeric gene mutations without clinically apparent disease in the VANISH Trial (28). A composite score including cardiac dimensions, cardiac biomarkers and surrogates for diastolic function was prospectively measured. There was a significantly better composite score in patients receiving valsartan when compared to placebo. This result was primarily driven by favorable N-terminal prohormone of brain natriuretic peptide (NT-proBNP) trends, tissue Doppler diastolic velocities, and LV end diastolic volume (28).

Mavacamten, a selective allosteric inhibitor of cardiac myocyte ATPase, improves myocardial energetics by reducing actin-myosin cross-bridge formation. In the phase 3 trial, patients on Mavacamten demonstrated greater improvement in New York Heart Association (NYHA) functional class and greater reductions in post-exercise LVOT gradient than those on placebo. Many patients also improved by NYHA class as well (29). Cardiac MRI in patients with HCM on Mavacamten demonstrated reduced LV mass index and reduced LV wall thickness (30). A recent study strikingly showed that after 16 weeks of therapy in patients that met criteria for septal reduction therapy, 77% of patients on placebo met criteria for septal reduction therapy or underwent the procedure compared to 18% of patients on Mavacamten P<0.001) (31). The United States Food and Drug Administration approved Mavacamten for treatment of obstructive HCM in symptomatic adults and unfortunately pediatric data are lacking at this time.

MEK inhibition and Noonan syndrome (NS)

NS is an autosomal dominant condition caused by hyperactivation of RAS/mitogen-activated protein kinase (MAPK) signal transduction pathway in about 85% of patients. Though there are other causes of the phenotypic presentation of NS that may not involve the RAS/MAPK pathway, the collective group are generally termed "RASopathies" (32). Many patients with NS have cardiovascular involvement including semilunar valve abnormalities and HCM. Infants with NS and HCM have elevated morbidity and mortality at one year of age compared to children with sarcomeric mutations, especially if heart failure occurs prior to 6 months of age (33,34).

Drugs to inhibit the RAS/MAPK signaling pathway, such as trametinib, cobimetinib, and binimetinib have been developed and approved for use in certain cancers. These drugs can potentially benefit patients with NS caused by mutations that result in gain-of-function changes in the RAS/MAPK pathway. This has been studied in murine models with mutation of RAF1 that can be seen in a small portion of patient with NS. Postnatal therapy with MEK

inhibition reversed hypertrophy, normalized cardiomyocyte size, and reduced fractional shortening more towards the normal range (35). Since that time there have been several case reports describing anecdotal improvements with MEK inhibition in patients with NS. Three groups have now described cases of four patients with observed improvement in patients with NS and HCM after use of trametinib (36-38). Additionally, studies have described resolution of arrhythmia and lymphatic abnormalities after initiation of MEK inhibition therapy (38-40). More investigation is needed in this domain, though there are some encouraging early reports of this medical therapy for a patient population commonly thought to only have cardiac transplantation as a therapeutic option (33).

Barth syndrome (BS)

BS is a rare genetic disorder, inherited in an X-linked recessive pattern, resulting in various phenotypic expressions of cardiomyopathy, skeletal myopathy, growth delay, and neutropenia. Cardiac findings in patients with BS can include DCM, HCM, endocardial fibroelastosis, LV non-compaction, ventricular arrhythmia, sudden cardiac death, and prolonged QTc interval (41). BS is caused by a loss-of-function mutation in the *TAZ* gene, which encodes for tafazzin, a phospholipid located in the mitochondrial membrane that plays a role in cardiolipin remodeling (42). Heart failure is a significant cause of mortality in these patients with 70% developing cardiomyopathy in their first year and 14% requiring heart transplantation (41).

Elamipretide is a mitochondria-targeting tetrapeptide that binds to cardiolipin and is thought to reduce the bioenergetic dysfunction (43). In addition to improved muscle strength and 6-minute walk test after long term therapy with elamipretide, improvement was seen in cardiac function with increased indexed stroke volume (43). Another promising therapy is bezafibrate, a peroxisome proliferator-activated receptor agonist, has been shown to significantly improve cardiac function in *TAZ* knockdown mice (44,45).

Duchenne muscular dystrophy

DMD is caused by mutations in the dystrophin gene, which plays a role in skeletal and cardiac muscle function, generally resulting in a truncated protein. The dystrophin gene is the largest known gene and as a result the mutations resulting in the DMD phenotype are diverse. It is characterized by progressive muscular atrophy with an associated cardiomyopathy that may progress to heart failure in some patients. Cardiac causes are the leading cause of mortality in the DMD population (46).

The goal of therapy in DMD has been to delay the onset of decline in skeletal and cardiac muscle function. As a result, patients are prophylactically treated with corticosteroids and ACE-i or ARB to promote favorable ventricular remodeling and slow the decline of function (47,48). MRA have also shown to attenuate the decline in cardiac function when added to ACE-i therapy (49,50). Beta blockade has shown conflicting results in the DMD population, though it is generally added after ACE-i and MRA (51).

Therapies directly targeting the underlying dystrophin deficiency are in various stages of development. These therapies target the most common dystrophin mutations—premature stop codons, and deletions. Eteplirsen is an exon-skipping drug that may improve myopathy by restoring production of dystrophin in patients with DMD who have a mutation amenable to exon 51 skipping (47). Clinical trials are ongoing, though one small study did show preserved cardiac function in a small cohort with no control arm over the 240-week study period (52). Ataluren works through stop codon readthrough and can benefit patients with DMD due to a nonsense mutation (53). It has conditional approval for use in the European Union and is under investigation with a multitude of clinical studies. Further research is needed to demonstrate the cardiac benefits of this drug. Viral gene therapy is also under investigation using adeno-associated virus to deliver micro-dystrophins.

Fabry cardiomyopathy

FD is caused by deficiency in activity of α-galactosidase A resulting in accumulation of glycolipid in many organs and tissues. Though many patients present in adulthood with symptoms, asymptomatic children that have yet to develop significant glycolipid deposits are prime targets for therapies that can prevent development of clinical disease. Italy and Taiwan have developed universal screening programs that have detected disease causing variants in 1 in 1,250 to 1 in 4,600 people screened, which is much higher than any previously cited population studies (54). Heart failure is the most common first cardiac event and cardiac complications are the main source of FD-related morbidity and mortality (54).

Available since 2001, enzyme replacement therapy (ERT) has been the standard treatment for most patients.

Unfortunately, this only delays the progression of FD and most patients develop antibodies of uncertain clinical significance to the biweekly infusions (55). Chaperone therapy is a more recent option for patients with FD due to certain mutations (56). Migalastat can be administered orally and acts as a pharmacologic chaperone in binding, stabilizing, and allowing proper lysosomal trafficking of α-galactosidase A enzyme for it to breakdown glycolipid (56). Patients treated for 18 months with Migalastat showed similar trajectories as those treated with ERT and there was a durable effect to 30 months (57). Second generation ERT and substrate reduction therapy are in varying stages of clinical study and may provide further benefit in attenuating and possibly reversing disease in the FD population (55).

Laminopathies

Striated muscle laminopathies are caused by various *LMNA* gene mutations resulting in DCM with or without varying degrees of muscular dystrophy (58). These mutations are inherited in an autosomal dominant manner and account for 5–8% of DCM (18). In a murine model as well as human hearts with *LMNA* DCM, p38a MAPK signaling has been shown to be hyperactive (59). This study also demonstrated that pharmacologic inhibition of p38a MAPK signaling significantly reduced LV dimensions and increased fractional shortening when compared to placebo therapy (59). Using this basis, a phase II study of ARRY-371797, a p38a inhibitor, in patients with symptomatic *LMNA*-related DCM (NCT02351856) has been completed and enrollment has begun in the phase III study (NCT03439514) with expected completion in 2024.

Single ventricle failure

Patients with single ventricle physiology are most at risk of developing heart failure within the congenital heart disease population and a focus has turned towards improving outcomes in these patients throughout the course of their disease. Survival after Fontan palliation continues to improve into the modern era with a more recent study reporting over 80% survival 20 years after surgery (60). An earlier study reported prevalence of heart failure, as defined by peak oxygen uptake (VO_2) <50% of predicted for age and sex, to be near 50% in the third decade of life (61). Studies evaluating medical therapy in the single ventricle population are lacking and recommendations are mostly in line with medical interventions shown to benefit patients with two ventricle circulation and systemic left ventricles (62).

A recent phase III trial showed that treatment over 26 weeks with udenafil, a phosphodiesterase-5 (PDE5) inhibitor, improved several measures of exercise capacity in teenagers with Fontan circulation and pre-existing peak VO_2 >50% (63). More study is needed to know if this will be a durable effect and if this will have any impact on patients with more significant exercise limitation. The development of vericiguat, a sGC stimulator, also has the potential to enhance the effect of PDE5 inhibitor therapy due to complimentary mechanisms of action, though this has not been studied.

More pre-clinical studies are being conducted to investigate the benefit of stem cell therapy in the earlier stages of single ventricle palliation. Cardiomyocyte proliferation rates in humans are reported to be 1% in the third decade and fall to 0.45% at age 75 (64). These rates are potentially higher in the neonatal heart with murine models showing potential for replenishing functional myocardium in the first week after birth (65). A phase II study using autologous cardiosphere-derived cells injected in coronary arteries 4 weeks after either stage II or stage III palliation showed improved ventricular function and reduced scar size when compared to controls three months after the experimental intervention (66). More rigorous studies with longer observation periods and larger sample sizes will be needed to confirm these benefits and a phase III trial (NCT02781922) is currently underway with completion expected in 2023.

Hydralazine/ISDN: precision medicine in the African ancestry population and pediatric experience

As our understanding of genetic diversity within the human population has grown, studying the benefit of specific therapies in different races has been of greater focus. Many clinical trials in heart failure therapy have represented patients that disproportionately skew towards the Caucasian race (67). An early study of ACE-i therapy that showed significant benefit in the Caucasian population did not show any benefit in patients of African descent (68). A study comparing hydralazine/ISDN combination with enalapril therapy showed similar reductions in mortality between the two groups (69). Hydralazine/ISDN has also shown significant benefit in treating African Americans with NYHA III or IV heart failure (70), though subsequent

reports showed significant underutilization in patients with African ancestry despite guideline recommendations (71). There are limited data in pediatrics though the ability to reduce blood pressure while preserving renal perfusion is appealing and a small retrospective analysis did show benefits with use of hydralazine/ISDN in a diverse pediatric patient population, most of which had heart failure (72).

Conclusions

The rapidly expanding understanding of the human genome and pharmacogenomics is leading to a flurry of diverse therapeutics for diseases with similar phenotypes and different genotypes. *Table 3* summarizes many of these completed and ongoing studies. Within pediatric heart failure specifically, the focus continues to shift from treating the maladaptive response to heart failure and the RAAS to gene-specific therapies with the potential to prevent and potentially reverse disease. Outside of the phenotype, a variety of factors must now be considered when selecting therapeutic option, from ethnicity/race, to the specific genetic cause of heart failure, to concurrent comorbid conditions, as well as the unique failure of the univentricular heart. Tailored therapies to the specific genotypes exist and for many conditions have recently proven benefit. Pediatric providers are in a unique position to begin therapies before significant pathology has developed and it will be of crucial importance for the pediatric clinician to keep abreast of this rapidly evolving reality of precision medicine that will dictate care for their patients.

Table 3 Summary of precision medicine therapies

Study	Therapy	Population	Type	Outcome	Length
Hypertrophic cardiomyopathy					
VANISH (28)	Valsartan *vs.* placebo	N=178	RCT	Trend towards less progression of hypertrophy (P=0.06), improved composite score	2 years
EXPLORER-HCM (29)	Mavacamten *vs.* placebo	HCM with LVOT gradient >50 mmHg and New York Heart Association class II–III (n=429 adults)	RCT	Reduction in post-exercise gradient (P<0.0001), increased pVO_2 (P=0.0006), improved symptoms (P<0.0001)	30 weeks
EXPLORER-HCM Substudy (30)	Mavacamten *vs.* placebo	N=35 adults	RCT	Decreased LV Mass Index (P<0.0001) and decreased LV wall thickness (–2.4 mm, P=0.008)	30 weeks
VALOR-HCM (31)	Mavacamten	HCM with LVOT obstruction meeting SRT criteria (n=112 adults)	RCT	82% no longer met SRT criteria *vs.* 23% (P<0.001)	16 weeks
Noonan cardiomyopathy					
Adelfinger *et al.* (36)	Trametinib	Two 3 months old	CS	Reduced hypertrophy, outflow gradient, and NT-proBNP	17 months
Mussa *et al.* (37)	Trametinib	47 days old	CR	Reduced hypertrophy, NT-proNP at 1 month. Worsened cardiac markers post-neurosurgery	2 months, deceased
Meisner *et al.* (38)	Trametinib	20 weeks old with atrial tachycardia	CR	Resolution of arrhythmia after 48 hours	6 months

Table 3 (*continued*)

Table 3 (*continued*)

Study	Therapy	Population	Type	Outcome	Length
Barth syndrome					
TAZPOWER (43)	Elamipretide	N=12 (12–35 years)	RCT	Improvement in 6MWT (P=0.024), increased stroke volume (P<0.01)	36 weeks
Huang *et al.* (44)	Bezafibrate	Mouse model	–	Preserved LV systolic function (P<0.001)	4 months
Schafer *et al.* (45)	Bezafibrate	Mouse model	–	Preserved LV systolic function (P<0.05)	4 months
Duchenne muscular dystrophy					
Schram *et al.* (48)	RAAS inhibition + steroid	N=86	COS	Fewer heart failure-related deaths (P=0.01), reduced rate of LV function decline	11 years
Alfano *et al.* (52)	Eteplirsen	N=12	RCT	Preserved LVEF	240 weeks
Fabry disease					
ATTRACT (57)	Migalastat	N=46 (18–72 years)	RCT	Reduced LV mass in patient with baseline LVH	30 months
Laminopathies					
Muchir *et al.* (59)	P38a MAPK inhibition	Mouse model	–	Prevents LV dilation and declining function	14 weeks
NCT03439514	ARRY-371797	–	RCT	Ongoing study	80 months
Single ventricle failure					
FUEL (63)	Udenafil	N=400 with Fontan physiology	RCT	Trend to improved VO_2 (P=0.071), improvement at ventilatory anaerobic threshold	26 weeks
PERSEUS (66)	Autologous cardiosphere-derived cells	N=41 undergoing stage 2 or 3 palliation	RCT	Improved ventricular function, heart failure and somatic growth (P<0.0001)	12 months
NCT02781922	Autologous cardiac stem cells	N=40 undergoing stage 2 or 3 palliation	RCT	Ongoing study	12 months

RCT, randomized controlled trial; HCM, hypertrophic cardiomyopathy; LVOT, left ventricular outflow tract; pVO_2, peak oxygen uptake; SRT, septal reduction therapy; CS, case series; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; CR, case report; 6MWT, 6-minute walk time; RAAS, renin-angiotensin aldosterone system; COS, cohort study; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LV, left ventricular; MAPK, mitogen-activated protein kinase.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-22-431/rc

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-22-431/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-22-431/coif). JG serves as an unpaid editorial board member of *Translational Pediatrics* from January 2023 to December 2024. He also serves as a

consultant to Daiichi Sankyo. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147-239.
2. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022;145:e895-e1032.
3. Hsu DT, Pearson GD. Heart failure in children: part I: history, etiology, and pathophysiology. Circ Heart Fail 2009;2:63-70.
4. Wetterstrand KA. DNA Sequencing Costs: Data. from the NHGRI Genome Sequencing Program. Available online: https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data
5. National Research Council (US) Committee on A Framework for Developing a New Taxonomy of Disease. Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease. Washington (DC): National Academies Press (US); 2011.
6. Masarone D, Valente F, Rubino M, et al. Pediatric Heart Failure: A Practical Guide to Diagnosis and Management. Pediatr Neonatol 2017;58:303-12.
7. Triposkiadis F, Karayannis G, Giamouzis G, et al. The sympathetic nervous system in heart failure physiology, pathophysiology, and clinical implications. J Am Coll Cardiol 2009;54:1747-62.
8. Unger T, Li J. The role of the renin-angiotensin-aldosterone system in heart failure. J Renin Angiotensin Aldosterone Syst 2004;5 Suppl 1:S7-10.
9. Das BB. Plasma B-type natriuretic peptides in children with cardiovascular diseases. Pediatr Cardiol 2010;31:1135-45.
10. Knecht M, Pagel I, Langenickel T, et al. Increased expression of renal neutral endopeptidase in severe heart failure. Life Sci 2002;71:2701-12.
11. Das BB. Current State of Pediatric Heart Failure. Children (Basel) 2018;5:88.
12. Braunwald E. The path to an angiotensin receptor antagonist-neprilysin inhibitor in the treatment of heart failure. J Am Coll Cardiol 2015;65:1029-41.
13. McNally EM, Golbus JR, Puckelwartz MJ. Genetic mutations and mechanisms in dilated cardiomyopathy. J Clin Invest 2013;123:19-26.
14. Dellefave-Castillo LM, Cirino AL, Callis TE, et al. Assessment of the Diagnostic Yield of Combined Cardiomyopathy and Arrhythmia Genetic Testing. JAMA Cardiol 2022;7:966-74.
15. Canepa M, Fumagalli C, Tini G, et al. Temporal Trend of Age at Diagnosis in Hypertrophic Cardiomyopathy: An Analysis of the International Sarcomeric Human Cardiomyopathy Registry. Circ Heart Fail 2020;13:e007230.
16. Marston NA, Han L, Olivotto I, et al. Clinical characteristics and outcomes in childhood-onset hypertrophic cardiomyopathy. Eur Heart J 2021;42:1988-96.
17. Lipshultz SE, Sleeper LA, Towbin JA, et al. The incidence of pediatric cardiomyopathy in two regions of the United States. N Engl J Med 2003;348:1647-55.
18. McNally EM, Mestroni L. Dilated Cardiomyopathy: Genetic Determinants and Mechanisms. Circ Res 2017;121:731-48.
19. Haas J, Frese KS, Peil B, et al. Atlas of the clinical genetics of human dilated cardiomyopathy. Eur Heart J 2015;36:1123-35a.
20. Towbin JA, Lowe AM, Colan SD, et al. Incidence, causes, and outcomes of dilated cardiomyopathy in children. JAMA 2006;296:1867-76.
21. Kaski JP, Syrris P, Burch M, et al. Idiopathic restrictive cardiomyopathy in children is caused by mutations in cardiac sarcomere protein genes. Heart 2008;94:1478-84.
22. Gallego-Delgado M, Delgado JF, Brossa-Loidi V, et al.

Idiopathic Restrictive Cardiomyopathy Is Primarily a Genetic Disease. J Am Coll Cardiol 2016;67:3021-3.
23. Liu MY, Zielonka B, Snarr BS, et al. Longitudinal Assessment of Outcome From Prenatal Diagnosis Through Fontan Operation for Over 500 Fetuses With Single Ventricle-Type Congenital Heart Disease: The Philadelphia Fetus-to-Fontan Cohort Study. J Am Heart Assoc 2018;7:e009145.
24. Toubat O, Kumar SR. Molecular Approaches in Single Ventricle Management. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2020;23:77-85.
25. Liu X, Yagi H, Saeed S, et al. The complex genetics of hypoplastic left heart syndrome. Nat Genet 2017;49:1152-9.
26. Teekakirikul P, Eminaga S, Toka O, et al. Cardiac fibrosis in mice with hypertrophic cardiomyopathy is mediated by non-myocyte proliferation and requires Tgf-β. J Clin Invest 2010;120:3520-9.
27. Maron MS, Olivotto I, Zenovich AG, et al. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. Circulation 2006;114:2232-9.
28. Ho CY, Day SM, Axelsson A, et al. Valsartan in early-stage hypertrophic cardiomyopathy: a randomized phase 2 trial. Nat Med 2021;27:1818-24.
29. Olivotto I, Oreziak A, Barriales-Villa R, et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2020;396:759-69.
30. Saberi S, Cardim N, Yamani M, et al. Mavacamten Favorably Impacts Cardiac Structure in Obstructive Hypertrophic Cardiomyopathy: EXPLORER-HCM Cardiac Magnetic Resonance Substudy Analysis. Circulation 2021;143:606-8.
31. Desai MY, Owens A, Geske JB, et al. Myosin Inhibition in Patients With Obstructive Hypertrophic Cardiomyopathy Referred for Septal Reduction Therapy. J Am Coll Cardiol 2022;80:95-108.
32. Linglart L, Gelb BD. Congenital heart defects in Noonan syndrome: Diagnosis, management, and treatment. Am J Med Genet C Semin Med Genet 2020;184:73-80.
33. Wilkinson JD, Lowe AM, Salbert BA, et al. Outcomes in children with Noonan syndrome and hypertrophic cardiomyopathy: a study from the Pediatric Cardiomyopathy Registry. Am Heart J 2012;164:442-8.
34. Kaltenecker E, Schleihauf J, Meierhofer C, et al. Long-term outcomes of childhood onset Noonan compared to sarcomere hypertrophic cardiomyopathy. Cardiovasc Diagn Ther 2019;9:S299-309.
35. Wu X, Simpson J, Hong JH, et al. MEK-ERK pathway modulation ameliorates disease phenotypes in a mouse model of Noonan syndrome associated with the Raf1(L613V) mutation. J Clin Invest 2011;121:1009-25.
36. Andelfinger G, Marquis C, Raboisson MJ, et al. Hypertrophic Cardiomyopathy in Noonan Syndrome Treated by MEK-Inhibition. J Am Coll Cardiol 2019;73:2237-9.
37. Mussa A, Carli D, Giorgio E, et al. MEK Inhibition in a Newborn with RAF1-Associated Noonan Syndrome Ameliorates Hypertrophic Cardiomyopathy but Is Insufficient to Revert Pulmonary Vascular Disease. Genes (Basel) 2021;13:6.
38. Meisner JK, Bradley DJ, Russell MW. Molecular Management of Multifocal Atrial Tachycardia in Noonan's Syndrome With MEK1/2 Inhibitor Trametinib. Circ Genom Precis Med 2021;14:e003327.
39. Dori Y, Smith C, Pinto E, et al. Severe Lymphatic Disorder Resolved With MEK Inhibition in a Patient With Noonan Syndrome and SOS1 Mutation. Pediatrics 2020;146:e20200167.
40. Nakano TA, Rankin AW, Annam A, et al. Trametinib for Refractory Chylous Effusions and Systemic Complications in Children with Noonan Syndrome. J Pediatr 2022;248:81-88.e1.
41. Clarke SL, Bowron A, Gonzalez IL, et al. Barth syndrome. Orphanet J Rare Dis 2013;8:23.
42. Jefferies JL. Barth syndrome. Am J Med Genet C Semin Med Genet 2013;163C:198-205.
43. Reid Thompson W, Hornby B, Manuel R, et al. A phase 2/3 randomized clinical trial followed by an open-label extension to evaluate the effectiveness of elamipretide in Barth syndrome, a genetic disorder of mitochondrial cardiolipin metabolism. Genet Med 2021;23:471-8.
44. Huang Y, Powers C, Moore V, et al. The PPAR pan-agonist bezafibrate ameliorates cardiomyopathy in a mouse model of Barth syndrome. Orphanet J Rare Dis 2017;12:49.
45. Schafer C, Moore V, Dasgupta N, et al. The Effects of PPAR Stimulation on Cardiac Metabolic Pathways in Barth Syndrome Mice. Front Pharmacol 2018;9:318.
46. Wittlieb-Weber CA, Knecht KR, Villa CR, et al. Risk Factors for Cardiac and Non-cardiac Causes of Death in Males with Duchenne Muscular Dystrophy. Pediatr Cardiol 2020;41:764-71.
47. Buddhe S, Cripe L, Friedland-Little J, et al. Cardiac

Management of the Patient With Duchenne Muscular Dystrophy. Pediatrics 2018;142:S72-81.
48. Schram G, Fournier A, Leduc H, et al. All-cause mortality and cardiovascular outcomes with prophylactic steroid therapy in Duchenne muscular dystrophy. J Am Coll Cardiol 2013;61:948-54.
49. Meyers TA, Townsend D. Cardiac Pathophysiology and the Future of Cardiac Therapies in Duchenne Muscular Dystrophy. Int J Mol Sci 2019;20:4098.
50. Raman SV, Hor KN, Mazur W, et al. Eplerenone for early cardiomyopathy in Duchenne muscular dystrophy: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 2015;14:153-61.
51. Adorisio R, Mencarelli E, Cantarutti N, et al. Duchenne Dilated Cardiomyopathy: Cardiac Management from Prevention to Advanced Cardiovascular Therapies. J Clin Med 2020;9:3186.
52. Alfano LN, Charleston JS, Connolly AM, et al. Long-term treatment with eteplirsen in nonambulatory patients with Duchenne muscular dystrophy. Medicine (Baltimore) 2019;98:e15858.
53. Łoboda A, Dulak J. Muscle and cardiac therapeutic strategies for Duchenne muscular dystrophy: past, present, and future. Pharmacol Rep 2020;72:1227-63.
54. Yim J, Yau O, Yeung DF, et al. Fabry Cardiomyopathy: Current Practice and Future Directions. Cells 2021;10:1532.
55. Vardarli I, Weber M, Rischpler C, et al. Fabry Cardiomyopathy: Current Treatment and Future Options. J Clin Med 2021;10:3026.
56. McCafferty EH, Scott LJ. Migalastat: A Review in Fabry Disease. Drugs 2019;79:543-54.
57. Feldt-Rasmussen U, Hughes D, Sunder-Plassmann G, et al. Long-term efficacy and safety of migalastat treatment in Fabry disease: 30-month results from the open-label extension of the randomized, phase 3 ATTRACT study. Mol Genet Metab 2020;131:219-28.
58. Benarroch L, Cohen E, Atalaia A, et al. Preclinical Advances of Therapies for Laminopathies. J Clin Med 2021;10:4834.
59. Muchir A, Wu W, Choi JC, et al. Abnormal p38α mitogen-activated protein kinase signaling in dilated cardiomyopathy caused by lamin A/C gene mutation. Hum Mol Genet 2012;21:4325-33.
60. Poh CL, d'Udekem Y. Life After Surviving Fontan Surgery: A Meta-Analysis of the Incidence and Predictors of Late Death. Heart Lung Circ 2018;27:552-9.
61. Diller GP, Giardini A, Dimopoulos K, et al. Predictors of morbidity and mortality in contemporary Fontan patients: results from a multicenter study including cardiopulmonary exercise testing in 321 patients. Eur Heart J 2010;31:3073-83.
62. Stout KK, Broberg CS, Book WM, et al. Chronic Heart Failure in Congenital Heart Disease: A Scientific Statement From the American Heart Association. Circulation 2016;133:770-801.
63. Goldberg DJ, Zak V, Goldstein BH, et al. Results of the FUEL Trial. Circulation 2020;141:641-51.
64. Bergmann O, Bhardwaj RD, Bernard S, et al. Evidence for cardiomyocyte renewal in humans. Science 2009;324:98-102.
65. Porrello ER, Mahmoud AI, Simpson E, et al. Transient regenerative potential of the neonatal mouse heart. Science 2011;331:1078-80.
66. Ishigami S, Ohtsuki S, Eitoku T, et al. Intracoronary Cardiac Progenitor Cells in Single Ventricle Physiology: The PERSEUS (Cardiac Progenitor Cell Infusion to Treat Univentricular Heart Disease) Randomized Phase 2 Trial. Circ Res 2017;120:1162-73.
67. Tillman F, Kim J, Makhlouf T, et al. A comprehensive review of chronic heart failure pharmacotherapy treatment approaches in African Americans. Ther Adv Cardiovasc Dis 2019;13:1753944719840192.
68. Exner DV, Dries DL, Domanski MJ, et al. Lesser response to angiotensin-converting-enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction. N Engl J Med 2001;344:1351-7.
69. Franciosa JA, Ferdinand KC, Yancy CW, et al. Treatment of heart failure in African Americans: a consensus statement. Congest Heart Fail 2010;16:27-38.
70. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med 2004;351:2049-57.
71. Brewster LM. Underuse of hydralazine and isosorbide dinitrate for heart failure in patients of African ancestry: a cross-European survey. ESC Heart Fail 2019;6:487-98.
72. Frandsen EL, Kirk CJ, Law YM, et al. Use of Isosorbide Dinitrate/Hydralazine in the Pediatric Cardiac Population. The Journal of Heart and Lung Transplantation 2021;40:S202-3.

Cite this article as: Valikodath N, Godown J, Sheybani A. Narrative review of pediatric heart failure in the age of precision medicine. Transl Pediatr 2023;12(3):503-513. doi: 10.21037/tp-22-431