Abstract: Pediatric cardiomyopathies are rare diseases with an annual incidence of 1.1 to 1.5 per 100,000. Dilated and hypertrophic cardiomyopathies are the most common; restrictive, noncompaction, and mixed cardiomyopathies occur infrequently; and arrhythmogenic right ventricular cardiomyopathy is rare. Pediatric cardiomyopathies can result from coronary artery abnormalities, tachyarrhythmias, exposure to infection or toxins, or secondary to other underlying disorders. Increasingly, the importance of genetic mutations in the pathogenesis of isolated or syndromic pediatric cardiomyopathies is becoming apparent. Pediatric cardiomyopathies often occur in the absence of comorbidities, such as atherosclerosis, hypertension, renal dysfunction, and diabetes mellitus; as a result, they offer insights into the primary pathogenesis of myocardial dysfunction. Large international registries have characterized the epidemiology, cause, and outcomes of pediatric cardiomyopathies. Although adult and pediatric cardiomyopathies have similar morphological and clinical manifestations, their outcomes differ significantly. Within 2 years of presentation, normalization of function occurs in 20% of children with dilated cardiomyopathy, and 40% die or undergo transplantation. Infants with hypertrophic cardiomyopathy have a 2-year mortality of 30%, whereas death is rare in older children. Sudden death is rare. Molecular evidence indicates that gene expression differs between adult and pediatric cardiomyopathies, suggesting that treatment response may differ as well. Clinical trials to support evidence-based treatments and the development of disease-specific therapies for pediatric cardiomyopathies are in their infancy. This compendium summarizes current knowledge of the genetic and molecular origins, clinical course, and outcomes of the most common phenotypic presentations of pediatric cardiomyopathies and highlights key areas where additional research is required.

Overview

Pediatric cardiomyopathies are rare diseases with an annual incidence of 1.1 to 1.5 per 100,000 in children <18 years old. Pediatric cardiomyopathies can result from coronary artery abnormalities, tachyarrhythmias, exposure to infection or toxins, or secondary to other underlying disorders. Because the accuracy and availability of genetic testing has increased, the importance of genetic mutations in the development of pediatric cardiomyopathies has become apparent. The study of pediatric cardiomyopathies offers important insights into the pathogenesis of myocardial dysfunction in the absence of confounding comorbidities common in adults, such as atherosclerosis, hypertension, renal dysfunction, and diabetes mellitus. The published literature in the field of pediatric cardiomyopathies ranges from large registry epidemiological outcome and risk factor analyses, to individual case reports. This compendium summarizes current knowledge of the genetic and molecular origins, clinical course, management guidelines, and outcomes of the most common phenotypic presentations of pediatric cardiomyopathies and highlights key areas where additional research is required.

Classification of Pediatric Cardiomyopathies

Cardiomyopathies are defined as abnormalities of the ventricular myocardium unexplained by abnormal loading conditions or congenital heart disease. The 1995 World Health Organization classifications were based on a combination of morphological (dilated and hypertrophic), physiological (restrictive), and etiologic (causes extrinsic to the myocardium, such as infection, were excluded) characteristics. The identification of genetic mutations has led to controversies on the classification criteria. The European Society of Cardiology and the American College of Cardiology/American Heart Association have proposed different definitions of hypertrophic cardiomyopathy (HCM)—with the European Society of Cardiology definition based on morphology and including both genetic mutations and secondary forms, and the American College of Cardiology/American Heart Association definition limiting HCM to only those found with sarcomeric mutations. The American College of Cardiology/American Heart Association classification cannot be universally applied to the pediatric cardiomyopathy population because genetic testing is not widely accepted, and the yield of testing in pediatric dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), and noncompaction cardiomyopathy (NCM) is low. In large population registries, pediatric cardiomyopathies have largely been defined by phenotypic characteristics, with cause, when known, added as a modifier.

In addition to the standard phenotypes of DCM, HCM, RCM, and NCM (Figures 1 through 4), a mixed category occurs in children and is an explicit recognition of phenotypic overlap that confounds attempts at a more specific categorization. For instance, HCM can be associated with severe hypokinesis in newborns with mitochondrial disorders, and sarcomeric HCM can transition to DCM. NCM can be seen in isolation or in combination with other phenotypes (NCM/HCM or NCM/DCM). Arrhythmogenic right ventricular cardiomyopathy is rarely diagnosed in the pediatric age group and thus will not be considered in this compendium.

Epidemiology

The Pediatric Cardiomyopathy Registry (PCMR) was first funded by the National Institutes of Health in 1994 and is the only national registry of its kind in North America. In the PCMR, DCM and HCM are the most common phenotypes with an annual incidence of 0.57 and 0.47 per 100,000 children, respectively. RCM has an incidence of 0.03 to 0.04 per 100,000 children and accounts for only 4.5% of pediatric cardiomyopathies with about 30% of patients having a mixed RCM/HCM phenotype. The incidence of NCM is estimated to be 0.12 per 100,000 in children from birth to 10 years old and ≤0.81 per 100,000 in infants from birth to 12 months old. In the PCMR, NCM accounted for 4.8% of pediatric cardiomyopathies, although more than twice as many children were diagnosed in the most recent era, suggesting that as the definition of NCM becomes standardized, the true incidence may be higher than previously appreciated. NCM may occur as an isolated phenotype (23%), a mixed NCM/DCM phenotype (59%), a mixed NCM/HCM phenotype (11%), or an indeterminate phenotype (8%).

Genetics

Pediatric cardiomyopathies are genetically heterogeneous with many different causative genes and multiple mutations in each gene. Variants in the same gene can cause different phenotypes (eg, variants in MYH7 can cause HCM and DCM), and variants in different genes can cause the same cardiomyopathy phenotype (eg, variants in MYH7 and MYBPC3 both cause HCM). Mutations in genes encoding components of the sarcomere or costamere and related binding proteins, Z-band, nuclear membrane, desmosome, mitochondriod, and calcium-handling proteins have all been found in children with cardiomyopathy. Genetic variants causing cardiomyopathy in children can also have systemic features affecting noncardiac organs. The RASopathies, including Noonan syndrome, are the most well-known syndromic causes of pediatric cardiomyopathy. Inborn errors of metabolism (CPT2 deficiency in DCM) and storage disorders (Pompe disease with HCM) are associated with childhood-onset cardiomyopathy. Congenital myopathies can present during childhood with both skeletal and heart muscle involvement; Duchenne muscular dystrophy is a classic example. Table 1 summarizes the common genes found in pediatric cardiomyopathies. The Genetic Testing Registry provides genetic test information.

There are multiple modes of inheritance for cardiomyopathies, including autosomal dominant, autosomal recessive,
Pediatric Cardiomyopathies

Isolated, autosomal-dominant cardiomyopathy is the most common genetic form of cardiomyopathy among individuals of all ages. There are shared genetic causes in children and adults, especially in families with autosomal-dominant cardiomyopathy. Variants can be inherited or occur de novo. The latter are particularly common in genes within the RAS pathway and among individuals presenting with severe, early-onset cardiomyopathies that are either fatal or require transplantation. Many autosomal dominantly inherited conditions have variable age of onset and penetrance.

**Dilated Cardiomyopathy**

**Definition:** Depressed ventricular function secondary to subnormal myocardial systolic shortening

**Incidence:** 0.57 cases per 100,000 children; over 50% of pediatric cardiomyopathies

**Genetic Causes**
- Sarcomere
- Costamere
- Z-band proteins
- Cytoskeletal
- Nucleoskeletal
- Desmosome
- Mitochondrial
- Calcium-handling
- Neuromuscular disorders
- Inborn errors of metabolism
- Genetic syndromes

**Disease Associations**
- Dominant mutations in the genes encoding the sarcomere
- Inflammation, either postinfectious or autoimmune
- Toxic exposure
- Neurohormonal abnormalities

**Symptoms**
- Presentation: Ranges from asymptomatic to acute decompensated heart failure and cardiogenic shock
- Arrhythmias: Especially increased with LMNA

**Treatments**
- Medical therapies to treat the symptoms of acute decompensated heart failure and to reverse the chronic effects of ventricular remodeling
- Mechanical support
- Heart transplantation

**Outcomes**
- Survival: Transplant-free survival ranges from 60% to 75% within 5 years after diagnosis with 20% to 45% of patients regaining normal cardiac function

---

**Hypertrophic Cardiomyopathy**

**Definition:** Intrinsic myocardial hypertrophy (not consequent to a hemodynamic stimulus)

**Incidence:** 0.47 cases per 100,000 children; 42% of pediatric cardiomyopathies

**Genetic Causes**
- Sarcomere
- RASopathies
- Metabolic
- Neurodegenerative disorders (Friedreich ataxia)
- Mitochondrial

**Disease Associations**
- Dominant mutations in the genes encoding the sarcomere
- Impaired energy use and resultant energy deficiency contributes to diastolic impairment
- Increase in collagen synthesis results in cardiac fibrosis
- Calcium mishandling

**Symptoms**
- Presentation: Ranges from asymptomatic +/- murmur to exercise intolerance, chest pain, palpitations, syncope, or cardiac arrest
- Sudden death: Increased risk during exercise

**Treatments**
- β blockade
- Calcium channel blockers
- Disopyramide
- Surgical myomectomy
- Automatic implantable cardioverter-defibrillator

**Outcomes**
- Survival: 97% 5-year and 94% 10-year survival
- Bimodal distribution in most studies, with a clustering of deaths before 1 year and again at 8 to 17 years

---

**Figure 1. Dilated cardiomyopathy.** End-diastolic apical 4-chamber (left) and parasternal short-axis end-diastolic (right) views of the left ventricle in a patient with severe dilated cardiomyopathy. The left ventricle is dilated and thin walled. The apical view also demonstrates the decreased mass:volume ratio with sphericalization (increased short-/long-axis ratio) of the left ventricle.

**Figure 2. Hypertrophic cardiomyopathy.** End-diastolic (left) and end-systolic (right) apical 4-chamber views of the left ventricle in a patient with severe hypertrophic cardiomyopathy. Regional left ventricular hypertrophy is most notable in the midseptum, lateral free wall, and lateral apex. The end-diastolic frame shows extension of the left ventricular cavity to the apex, and the end-systolic frame shows systolic apical obliteration.
both within and between families. Digenic and autosomal recessive inheritance for typical, adult, autosomal-dominant causes of cardiomyopathy has been described in children with early and severe presentations. The identification of multiple variants in ≥1 genes, however, explains only a small fraction of the observed clinical variability among affected individuals. Several studies have investigated the role of nonsarcomeric polymorphisms as potential disease modifiers, yet, additional studies are needed to replicate and further explore potential impact on disease. In general, there is limited understanding of genetic, environmental, and other, as of yet undiscovered, modifying factors in pediatric cardiomyopathy.

**Figure 3. Restrictive cardiomyopathy.** End-systolic apical 4-chamber view of the left and right ventricles in a patient with restrictive cardiomyopathy demonstrating mildly small right and left ventricular cavities with massive biatrial dilation.

**Figure 4. Noncompaction cardiomyopathy.** End-diastolic apical 4-chamber view of the left ventricular in a patient with noncompaction, demonstrating multiple finger-like protrusions of myocardial trabeculations into the apex, resulting in deep intertrabecular interstices.
<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Inheritance</th>
<th>Associated Cardiac Phenotype(s)</th>
<th>Additional Phenotype(s)</th>
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<tr>
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</table>

(Continued)
The increased availability of genetic testing has led to increasing detection of genetic causes in pediatric patients. In PCMR data published in 2003, approximately one third of children with cardiomyopathy had a confirmed cause. Diagnostic categories included myocarditis (16% DCM), metabolic (4% DCM, 9% HCM), syndromic (1% DCM, 9% HCM), neuromuscular (9% DCM, 9% HCM), familial (5% DCM), and idiopathic. A more recent single-center study, incorporating clinical genetic evaluation and testing, identified an underlying cause in ≈75% of affected children (excluding those with neuromuscular disease): 42% familial, 20.5% metabolic, and 14.5% syndromic with the remainder being idiopathic. Although genetic testing and evaluation have improved the ability to identify underlying cause, diagnostic rates in clinical practice remain uncertain because genetic testing is not routinely and universally incorporated into the clinical care of children with cardiomyopathy.

Published guidelines have recommended approaches for genetic testing and family screening in patients with isolated, autosomal-dominant cardiomyopathy. These guidelines do not specifically address many circumstances commonly encountered in children, and both the timing and type of genetic testing in children vary by the clinical context. Phenotype-specific gene panels are the most appropriate baseline test for isolated cardiomyopathy (eg, HCM gene panel). The size of these panels varies by clinical genetic testing laboratory and phenotype. Although the number of genes has increased, the overall test sensitivity has not, suggesting that expanding from phenotype-specific gene panel testing to a larger panel or whole-exome sequencing has limited use in most cases. In the context of a complex phenotype, whole-exome sequencing may be considered.

Genetic testing should be guided by the medical and family histories, ideally by teams experienced in caring for children with cardiomyopathy (Figure 5). Not surprisingly, individuals with a positive family history of cardiomyopathy have a higher diagnostic yield with testing. Currently, clinical gene panel tests detect disease-causing variants in ≤60% of children with HCM but are informative in <25% of children with DCM, NCM, or RCM. If a causal genetic variant is identified, cascade genetic testing can be recommended for at-risk relatives. Genetic screening of family members requires

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Inheritance</th>
<th>Associated Cardiac Phenotype(s)</th>
<th>Additional Phenotype(s)</th>
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<td>PTPN11</td>
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<td>SOS1</td>
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<td>SPRED1</td>
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<tbody>
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</tr>
<tr>
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<tr>
<td>HADHA</td>
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<tr>
<td>LAMP2</td>
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<tr>
<td>MT-TL1</td>
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<tr>
<td>PRKAG2</td>
</tr>
<tr>
<td>SLC22A5</td>
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<td>TAZ</td>
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<th>Neuromuscular/neurodegenerative disorders</th>
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<tbody>
<tr>
<td>DMD</td>
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<tr>
<td>FRDA1</td>
</tr>
</tbody>
</table>

AD indicates autosomal dominant; AR, autosomal recessive; ARVC arrhythmogenic right ventricular cardiomyopathy; CFC, cardiofaciocutaneous; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; NCM, noncompaction cardiomyopathy; and RCM, restrictive cardiomyopathy.
expertise and resources that may not be available in all practice settings. In centers with personnel and resources dedicated to family-based screening, 39% to 66% of at-risk relatives completed recommended genetic testing, and 57% completed cardiac screening.40,41 Even in families with multiple affected relatives, genetic testing does not always identify a causal variant, suggesting the presence of missed variants, genes not yet identified, or complex gene-to-gene and gene-to-environment interactions. Environmental and infectious factors either causing or contributing to cardiomyopathy may be present, particularly in children with DCM. Copy number variation analysis has been performed for genes known to cause cardiomyopathy, and data suggest that deletions and duplications account for only a minority of cases.42 It may be that smaller base pair deletions or intronic sequence variants are missed because of limitations at the technological or bioinformatic level. With increasing access to genomic analysis of pediatric cardiomyopathy cases, including exome/genome sequencing, additional single gene causes are likely to be identified.

### Medical Evaluation

In DCM, 75% to 80% of children present with signs and symptoms of heart failure, whereas only 20% of infants and 4% of older children with HCM present with overt heart failure.1,15,43 Signs and symptoms of biventricular failure are more common in children compared with adults. Infants and young children present with poor feeding, growth failure, tachypnea, and hepatomegaly, whereas older children present with abdominal symptoms because of hepatomegaly and low cardiac output.44 Grading heart failure symptoms in infants and children can be challenging because the New York Heart Association class is not applicable. Thus, the Ross Heart Failure class, which defines symptoms based on respiratory distress, feeding intolerance, and failure to thrive, has been adopted but has not been validated against outcomes.45 Heart failure with preserved ejection fraction can be found in patients with HCM, RCM, and NCM. These patients often have symptoms related to diastolic dysfunction and poor cardiac output, including dyspnea, orthopnea, and growth failure.

In addition to clinically assessing for heart failure, evaluating the child with cardiomyopathy includes searching for...
an underlying metabolic, congenital, or acquired cause. This is particularly important in the infant population, where the incidence of metabolic disease is greater and includes potentially reversible conditions, such as primary carnitine deficiency. A thorough medical history, including growth and development, developmental milestone assessment, chronic medical problem review, and a 3-generation pedigree should be performed, as well as comprehensive physical examination attending to features suggesting a genetic syndrome (Table 2). This evaluation can be extensive, and many centers have gone to a staged approach based on the age at presentation and clinical history and with the involvement of a multidisciplinary team, including geneticists and neurologists.38,46,47

Echocardiography establishes the cardiac phenotype and is performed serially to aid in prognosis and treatment. In children with DCM, the degree of ventricular dysfunction and dilation is a strong predictor of death or transplantation.36,49 In patients with HCM, septal wall thickness has been associated with sudden death and echocardiography is also the primary method of assessing the severity and progression of hypertrophy, left ventricular outflow tract obstruction, and of evaluating systolic and diastolic performance.49 Cardiac magnetic resonance imaging has been useful to evaluate for inflammatory processes and late gadolinium enhancement, which can further define cause and assist in management and risk stratification.50–52 The use of cardiac biomarkers, including B-type natriuretic peptide in DCM, have been helpful in evaluating inflammatory processes and late gadolinium enhancement, which can further define cause and assist in management and risk stratification.50–52

### Table 2. Clinical Considerations for Evaluation of Cause

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<tr>
<th>History</th>
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<td>Feeding difficulties or intolerance</td>
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<td></td>
<td>Seizures</td>
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<td>Metabolic decompensation with illness</td>
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<td>Vision or hearing loss</td>
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<td></td>
<td>Hypotonia or hypertonia</td>
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<td></td>
<td>Gait abnormalities or muscle weakness</td>
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<td>Congenital anomaly</td>
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<tr>
<td>Laboratory</td>
<td>Urine organic acids, serum amino acids, acylcarnitine profile, lactate, pyruvate, creatine phosphokinase, enzyme testing for concern of Pompe</td>
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<tr>
<td></td>
<td>Sequence-based genetic testing (eg, cardiomyopathy panel testing, Noonan syndrome testing, mitochondrial panel)</td>
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<tr>
<td></td>
<td>Directed biochemical (eg, urine glycosaminoglycans, transferrin isoelectric focusing), genetic (eg, muscular dystrophy panel), or invasive testing (eg, muscle biopsy) based on initial laboratory results</td>
</tr>
</tbody>
</table>

### Dilated Cardiomyopathy

#### Molecular Genetics of DCM

Between 35% and 40% of genetic DCM cases are thought to be caused by sarcomere gene mutations, with mutations in the giant protein titin estimated to be responsible for about 25%.37,58 Gene mutations can also affect multiple Z-band proteins, which connect the thin filaments and titin, thereby serving as an important nodal point of mechanosignaling.59,60 Mutations in members of the LINC (linker of nucleoskeleton and cytoskeleton) complex, that links the nucleus to the cytoplasm, have been described in pediatric DCM, including the lamin A/C proteins, emerin, and nesprins-1 and -2.61,62 Both lamin A/C and emerin-null fibroblasts have altered expression of mechanosensitive genes in response to mechanical stress.62 Although genotype–phenotype correlations are lacking for most cases of DCM, mutations in genes such as LMNA (and DES) are known to be highly associated with conduction system disease (sinoatrial node disease, atrial arrhythmias, atrioventricular heart block, and ventricular tachyarrhythmias). Thus, the presence of these genes is a risk factor for sudden death.25–46 Mutations in dystrophin and the sarcoglycans produce skeletal muscle disease and cardiomyopathy; as such, heart failure in these patients may be further compromised by hyperventilation from respiratory muscle weakness.67

#### Inflammatory Causes of DCM

Evidence of viral myocarditis is common in children with DCM. From registry data, between 35% and 48% of children with DCM who undergo endomyocardial biopsy have evidence of myocarditis.68–70 Parvovirus B19, influenza, Epstein–Barr, HIV, coxsackie virus, herpes, and adenovirus have all been identified.69–73 Murine models of myocarditis (coxsackie or adenoviral) demonstrate evidence of disruption of several important pathways in the innate and activated immune systems.74,75 The enteroviral protease 2A has been demonstrated to cleave the cytoskeletal protein dystrophin which results in severe DCM.76–77 Genetic mutations in the dystrophin gene have been demonstrated in Duchenne muscular dystrophy and other X-linked forms of DCM, creating a link between the acquired and genetic forms of DCM.78

#### Toxic Causes of DCM

Pediatric DCM can occur after exposure to toxins, such as anthracycline exposure during chemotherapy. The mechanism of anthracycline-induced injury is incompletely understood, but oxidative stress and reactive oxygen species activation are felt to play a key role in cell damage.79 Radiation exposure and genetic polymorphisms have been associated with a higher frequency of anthracycline toxicity.80,81 Survivors of childhood cancer are 6× more likely than their siblings to develop congestive heart failure.82 The cumulative incidence of heart failure in childhood cancer survivors has been difficult to accurately determine, but recent estimates are 4% to 5% over a 20- to 30-year period.82–84 Risk factors for heart failure include female sex, young age at diagnosis, treatment during the 1980s, and total anthracycline or radiation dose.85–86 The relative hazard of congestive heart failure with anthracycline treatment was 2.4-fold for doses <250 mg/m² and 5.2-fold for doses >250 mg/m².83
Neurohormonal Activation in DCM

The role of neurohormonal activation in the pathophysiology of chronic heart failure in adults is well described. The neurohormonal derangements in pediatric DCM are described in small series and include elevations in circulating norepinephrine,83 and activation of the renin-angiotensin system, decreased, aldosterone, and sympathetic nervous system activation with carvedilol treatment.88 There is some evidence that the cardiac molecular response to stress in pediatric DCM is distinct from adult DCM. Tissue analysis of explanted hearts found downregulation of β-2 adrenergic receptors and upregulation of connexin-43 in pediatric DCM, whereas upregulation of the β-2 adrenergic receptor and downregulation of connexin-43 were found in adult DCM.89 In addition, phosphatase expression and phosphorylation of phospholamban were unchanged in pediatric DCM, whereas adult DCM hearts had upregulation in phosphatase expression and decreased phosphorylation of phospholamban.89 In another study, expression of adenylyl cyclase and phosphodiesterase isoforms after treatment with a phosphodiesterase-3 inhibitor also differed between pediatric and adult explanted DCM hearts.90 Treatment of human-induced pluripotent stem cell–derived cardiomyocytes and neonatal rat ventricular myocytes with serum from pediatric DCM patients showed pathogenic changes in gene expression independent of the renin–angiotensin–aldosterone and adrenergic systems.91 These data suggest that the response to adult heart failure therapies targeting the neurohormonal system may be different in pediatric DCM and also suggest the possibility of identifying therapeutic targets specific to pediatric DCM.

Clinical Concepts in DCM

Presentation

The clinical presentation of children with DCM ranges from asymptomatic to acute decompensated heart failure and cardiogenic shock.92 Many children require hospitalization at the time of diagnosis because of advanced heart failure.93,94 In a large population-based study of admissions for new-onset heart failure in children with cardiomyopathy, 54% received intravenous inotropic support, 41% were placed on mechanical ventilation, 13% were treated with extracorporeal membrane oxygenation, and 11% underwent urgent transplantation.94 Compared with adults, children with cardiomyopathy hospitalized with heart failure had greater morbidity and mortality and used advanced heart failure therapies more frequently.95 In patients with DCM as a component of a multisystem disease (eg, neuromuscular, metabolic, and mitochondrial disorders), the underlying disease is often an important determinant of patient outcome.1,3,15

Comorbid conditions are also key contributors to morbidity and mortality in pediatric DCM.96 Hyponatremia occurs in nearly half of children presenting with acute heart failure, and anemia may occur in ≤40% of patients; both factors are associated with death, transplant, and mechanical circulatory support.97,98 Additional serious comorbidities, such as sepsis, acute renal failure, and respiratory failure, are less common but are strongly associated with mortality.98 It is not clear whether comorbidities are a consequence of worse heart failure or causative. The effectiveness of treatment interventions targeting modifiable comorbidities has not been studied and is an area of research need.

Outcomes and Risk Prediction

The outcome after presentation with DCM in children is by no means certain, with some patients requiring urgent mechanical assist support followed by transplantation and others regaining normal function, despite presenting with fulminant heart failure.99,100 Registries from the United States, Australia, and Europe report transplant-free survival rates ranging from 60% to 75% within 5 years after diagnosis, with most events occurring within 2 years of presentation.4,10,15,101–103 These same registries also report that 20% to 45% of patients regain normal cardiac function during the same time period.4,10,99,101,102

Risk factor analyses have confirmed several obvious predictors of worse outcome, such as the worse heart failure, ejection fraction, and ventricular dilation, along with other factors, such as older age (>6) and higher B-type natriuretic peptide concentrations.48,53,100 B-type natriuretic peptide levels at hospital admission may be less important than the level when clinically stable or the change in levels with therapy.54,55 More specific biomarkers are needed to distinguish patients at highest risk death from those likely to recover. Potential targets for investigation include genetic variants, circulating or imaging markers of inflammation or stress, neurohormonal abnormalities, microRNA, viral genome on endomyocardial biopsy, and markers of extracardiac impairment.50,69,70,97,99,104,105 Identifying biomarkers that are important for pediatric patients is the focus of a large ongoing study by the PCMR and is an area of research need.

Medical Management

The follow-up and management of pediatric DCM is challenging because invasive strategies, such as mechanical support or transplantation, must be weighed against the possibility of full recovery. Although acute and chronic adult heart failure therapies are routinely applied to children with DCM (Table 3), extrapolating the evidence for treatment efficacy from adults to children is fraught with difficulties given the significant differences in age, cause, comorbidities, and outcomes between the 2 populations.108 Studies of heart failure medications in pediatric DCM are limited, with few supporting a treatment strategy and some studies suggesting no benefit.103,107 Drug trials in pediatric cardiomyopathy are challenging because of limitations in power because of small sample size, lack of validated end points, and incomplete pharmacokinetic/pharmacodynamic data.106,108,109 A current study of sacubitril/valsartan in children is using a novel global rank end point as the primary outcome.110 If successful, this may prove to be a useful end point design of future studies. Identifying appropriate surrogate outcomes and developing accurate pharmacokinetic and pharmacodynamic models are the key research areas needed to advance the development of new heart failure agents in pediatric DCM.

Mechanical Support and Transplantation

Contemporary outcomes after heart transplantation in children with DCM are excellent, with a 1-year survival of 94%.111 The use of mechanical support to bridge patients to heart transplantation is increasing, because of an increasing
number of children being listed and an increasing wait time. There have been several novel approaches to the treatment of DCM that are relevant to the pediatric population. A small study of pulmonary artery banding in children with DCM reported clinical improvement occurred in 8 of 10 patients (detailed for transplant or improved left ventricular function). The rationale for the improvement includes an increase right ventricular pressure that alters right and left ventricular interaction and decreases mitral regurgitation. Human mesenchymal stem cells have antifibrotic, proregenerative, and anti-inflammatory effects—all features that argue for a therapeutic effect in pediatric DCM. A small adult trial in nonischemic DCM has demonstrated a favorable safety profile with better quality of life and lower adverse event scores after transendocardial injection of allogenic stem cells. Another small trial has demonstrated increased left ventricular ejection fraction with better functional and clinical outcome after intramyocardial stem cell injection.

### Hypertrophic Cardiomyopathy

#### Molecular Genetics of HCM

HCM was the first cardiac disease to be described at the molecular level when a disease-causing mutation in the β-myosin heavy chain was discovered. Since then, >1400 mutations in different sarcomeric genes have been identified. Mutations, primarily missense, in the MYBPC3 and MYH7 genes are found in about 70% of HCM cases of all ages. Overall penetrance of the disease is unpredictable but may be age dependent with highly variable expression. In infants and children with HCM, nonsarcomeric HCM phenotypes have more diverse genetic causes and include the RASopathies, metabolic storage disorders, neurodegenerative disorders (Friedreich ataxia), and mitochondrial disorders (Table 1).

#### Clinical Concepts in HCM

##### Presentation

HCM caused by inborn errors of metabolism and malformation syndromes generally presents in infancy and is often associated with neurological and musculoskeletal abnormalities. HCM from sarcomeric mutations is commonly diagnosed during adolescence or early adulthood, although onset can occur from fetal life onward. HCM can also be diagnosed in asymptomatic individuals from testing performed for other reasons or at the time of screening in first-degree relatives. Symptoms of heart failure are rare in the older child. Progressive left atrial enlargement can occur as a result of diastolic dysfunction and predisposes the HCM patient to atrial arrhythmias. Cardiac arrest or sudden death may be the presenting event in a previously healthy child. Older children may experience progressive left ventricular dysfunction and dilatation with a transition to DCM and chronic heart failure. Recently, the HCMNet Study has shown that HCM mutation carriers have abnormal echocardiographic findings despite a negative phenotype (no hypertrophy).

##### Outcomes and Risk Prediction

Overall survival for pediatric HCM is 97% at 5 years and 94% at 10 years after presentation. The age at death in children with HCM peaks before 1 year of age and again at 8 to 17 years of age.

### Disease-Specific Therapies in DCM

If an inborn error of metabolism is diagnosed, treatment strategies can be directed toward the underlying metabolic abnormality and may include dietary management and supplementation to decrease the accumulation of toxic metabolic by-products. Specific management is also directed toward avoiding metabolic or energetic crises. Supplementation with carnitine in primary carnitine deficiency cures DCM, emphasizing the critical need to diagnose this disease promptly. Duchenne muscular dystrophy is one of the rare genetic DCM diseases with a substantial focus on gene-directed therapies, including viral vector delivery of minigenes, exon-skipping approaches, and nonsense suppression therapy. CRISPR/Cas9 technology has been used to remove the mutation in the dystrophin gene and thereby modulates protein expression in mouse models. These approaches may have broader application to other genetic causes of DCM.
transplantation was significantly increased when ≥2 risk factors were present. Identifying patients at risk for ventricular arrhythmias is important in risk stratification of adult HCM patients; however, the association of specific arrhythmia patterns with the risk of sudden death has not been described in children. In adults, cardiac magnetic resonance imaging may be more accurate than echocardiography at measuring wall thickness, and late gadolinium enhancement can delineate the amount of scar tissue which may predict a poor clinical outcome, but this has not been studied in children with HCM.

Better risk stratification to identify patients at risk for worse outcome is needed in pediatric HCM. In adult HCM patients, a blunted blood pressure response on exercise testing and elevations in cardiac troponins has been identified as risk factors for worse outcome, but these have not been evaluated in children. Biomarkers such as B-type natriuretic peptide or markers of myocardial scarring have not been studied rigorously in children. Population-based data combining imaging, arrhythmia monitoring, biomarker testing, and exercise testing would help refine risk groups and if validated could serve as surrogate endpoints for treatment trials.

Medical Management

The treatment goals for children with HCM include relieving symptoms and preventing sudden death. General measures include maintaining adequate hydration and avoiding situations and medications that cause marked peripheral vasodilation. Medical therapy for treating symptoms in pediatric HCM has not been rigorously studied; thus, treatment strategies are extrapolated from adult studies. β-blockade is used to treat symptomatic children with HCM and outflow tract obstruction, and few small studies suggest that β-blockade may reduce the risk of sudden unexpected death in asymptomatic children prompting the routine use in many centers. If patients cannot tolerate β-blockade, or if β-blockade does not alleviate symptoms, a calcium channel blocker, specifically verapamil, is often added or substituted. Disopyramide may be used in symptom-resistant patients, but children may not tolerate the side effects. Diuretics are used cautiously when reactive pulmonary edema limits mobility. Studies of the efficacy and optimal doses of the various medical therapies used in pediatric HCM are areas of great research need.

Patients with HCM are at increased risk of sudden death during exercise and are therefore advised to stop participating in competitive sports. Restricting sports participation during adolescence puts patients at risk for social isolation, depression, suicide, obesity, and loss of posthigh school educational opportunities. Restricting sports participation in HCM has not been shown to improve survival, in part because randomized testing of this hypothesis is at best impractical and is considered by many to be unethical. Regular exercise is likely beneficial in HCM, but the level of exercise at which this benefit is gained is not known with certainty. The LIVHECM study (Lifestyle and Exercise in Hypertrophic Cardiomyopathy Study) is an observational study evaluating the risk and benefits of exercise and sports participation on cardiac events and quality of life in patients with HCM as young as 8 years old. The follow-up period is 3 years, but longer follow-up is likely needed to more accurately assess risk.

Surgical myectomy to relieve left ventricular outflow obstruction is considered when symptoms persist despite medications, the left ventricular outflow gradient exceeds 60 to 70 mm Hg at rest, or mitral regurgitation increases. In children and young adults, gradient relief is effective, and symptom improvement is excellent. The benefits of myectomy also include improving mitral regurgitation by decreasing systolic anterior motion of the mitral valve, although there may be an increased risk of aortic or mitral valve injury in children.

Automatic implantable cardioverter–defibrillator (AICD) implantation in adults with HCM has substantially decreased mortality. Children with HCM have much lower incidence of sudden cardiac death when compared with adults, and sudden death in pediatric HCM before adolescence is rare. Risk factors for sudden death in adults have not been validated in children; thus, there is a pressing need for data to support pediatric HCM-specific guidelines for AICD use to maximize the benefit of AICD use and to minimize risk. Given the low event rate, a large, multicenter, prospective observational registry that includes long-term, comprehensive data collection is needed.

Disease-Specific Therapies in HCM

The infantile form of Pompe disease presents in the first few months with severe HCM, failure to thrive, hypotonia, and respiratory failure. Enzyme replacement therapy is most effective when started early and is associated with decreased cardiac hypertrophy. Certain lysosomal storage diseases, specifically mucopolysaccharidosis I, II, IV, and VI, are also currently treated with enzyme replacement therapy or bone marrow transplantation. Results are variable and early treatment seems to be associated with better outcomes.

Pharmacological interventions in rodent models of HCM have demonstrated prevention or attenuation of hypertrophy before full expression of the phenotype. Screening of first-degree relatives for HCM can identify children in whom preemptive therapy may favorably modify disease expression. A study of diltiazem was performed in genotype-positive/phenotype-negative children and demonstrated slower progression of echocardiographic markers of disease. Another multicenter clinical trial using valsartan in a similar population is currently in progress (VANISH trial [Valsartan for Attenuating Disease Evolution In Early Sarcomeric HCM]).

HCM in patients with RASopathies presents earlier and can be more rapidly progressive than HCM caused by sarcomeric mutations, and heart failure symptoms and left ventricular outflow tract obstruction are common. A PCMR study showed that children with Noonan syndrome (compared with HCM from other causes) were far more likely to present before the age of 6 months (51% versus 28%), more likely to present with...
Restrictive Cardiomyopathy

Molecular Genetics of RCM

The most common genes implicated in RCM are sarcomeric, including the troponin I (TNNI3), β-myosin heavy chain (MYH7), α cardiac actin (ACTC1), titin (TTN), and myosin light chain genes. Several nonsarcomeric gene abnormalities also cause RCM. The desmin gene (DES), which encodes the chief intermediate filament of skeletal and cardiac muscle, has been associated with RCM. Desmin mutations are also associated with conduction abnormalities, including high-grade atrioventricular block. Mutations affecting calcium homeostasis within the sarcomere have also been described. In the end, the phenotype relies on sarcomere functional abnormalities, similar to those in HCM. Cardiomyocyte alterations and their persistent responses at the cellular level also cause changes that are correlated with sudden cardiac death and other cardiac problems.

Clinical Concepts in RCM

Presentation

The clinical presentation of pediatric RCM varies, ranging from no symptoms to overt heart failure, syncope, or sudden death. Age at diagnosis ranges from early infancy through late adulthood. Nearly, a quarter of RCM patients have a family history of cardiomyopathy. A third of patients with RCM have a mixed phenotype with characteristics of RCM and HCM. Many of the clinical manifestations of RCM are the result of elevated filling pressures that cause pulmonary edema, pulmonary hypertension, hepatomegaly, and peripheral edema. Children with RCM may have a history of reactive airway disease or frequent respiratory infections that prompt referral to cardiology after a chest radiograph shows cardiomegaly. Syncope is an ominous presenting manifestation, presumably caused by ischemia, arrhythmia, or thromboembolism, and increases the risk of sudden death. Enlarged atria increase the risk of clot formation and stroke in addition to atrial arrhythmias. Patients are also at risk of sudden cardiac death from ventricular arrhythmia or heart block. In the later stages of disease, systolic function may fail. Although cardiac magnetic resonance imaging may help distinguish RCM from constrictive pericarditis and infiltrative disease (eg, amyloidosis, sarcoidosis, and hemochromatosis) in adults, its diagnostic usefulness in children is minimal given that these other diagnoses are rarely seen in the pediatric age group. Cardiac catheterization is an excellent method to distinguish RCM from constrictive pericarditis. In addition, it can assess the degree of abnormal left and right heart filling pressures and pulmonary hypertension.

Outcomes and Risk Prediction

Children with RCM have notably poor outcomes. In the largest cohort study to date, 5-year survival from the diagnosis of RCM was 68%. Transplant-free survival in children with pure RCM is worse than in children with a mixed RCM/HCM phenotype, with 1- and 5-year survivals of 48% and 22% versus 77% and 68%, respectively. Congestive heart failure and lower shortening fraction z-score at presentation in all RCM patients and higher posterior wall thickness z-score in the mixed RCM/HCM phenotype predicted worse outcomes. Arrhythmia monitoring is necessary to identify patients with conduction disturbances or tachyarrhythmias. Atrial or ventricular arrhythmias, ischemic changes, or pulmonary hypertension predict worse outcomes. Pulmonary hypertension can develop rapidly in patients with RCM in the absence of significant heart failure.

Medical Management

No medical therapies have been described to treat diastolic dysfunction in RCM. Diuretics can improve pulmonary and systemic venous congestion but must be balanced with the need to maintain adequate preload. Anticoagulation should be considered to avoid clot formation in the atria and prevent thromboembolic events. Arrhythmias can be treated with antiarrhythmia medications and AICD placement, but the effectiveness of these therapies is not well described.

Transplantation

Given the limited medical therapies, poor mechanical support options, and the absence of risk factors that consistently predict rapid disease progression or sudden death, early consideration for heart transplantation has been promoted for RCM patients. Overall waitlist mortality for children with RCM is low, at 10%. Children requiring mechanical support and infants have a significantly higher risk of death while on the waitlist. After transplantation, 1- and 5-year survival is 89% and 77%, respectively. Overall survival 10 years after transplantation is similar to that of children receiving transplants for other forms of cardiomyopathy. Better methods of risk stratification to identify patients who would benefit from early heart transplantation are needed.

Disease-Specific Therapies in RCM

Although medical therapies that treat diastolic dysfunction are lacking, the genetic characterization of RCM has improved understanding of the pathways involved in the development of RCM and may offer insights into potential disease-specific therapeutic targets. Mutations in the desmin gene have been found in areas of the gene that are critically relevant for filament assembly and interaction with other cytoskeletal proteins. Multiple mutations in the sarcomeric genes have been identified in RCM that potentially disrupt the actin-binding domain of troponin I and areas of the tropomyosin-binding domain through mechanisms that may increase calcium sensitivity of contraction and the cooperatively of thin filament interactions. A knockin murine model of mutant myopalladin that results in RCM demonstrated changes in the mechanosensory proteins without contractile impairment, which may explain why medical therapies that target β-receptors or the renin–angiotensin–aldosterone system pathway are not effective in RCM.

Noncompaction Cardiomyopathy

Molecular Genetics of NCM

Noncompaction of the left ventricle is a common finding in Barth syndrome, an X-linked recessive disorder caused by a
mutation in the tafazzin (TAZ) gene on chromosome Xq28. Presentation is commonly mixed in association with DCM.\textsuperscript{158} In addition, other inborn errors of metabolism, including glycogen storage disease type 1b, malonyl coenzyme A decarboxylase deficiency, and cobalamin C deficiency, have been reported with NCM. Although specific genetic mutations have not been identified, NCM can occur with any form of congenital heart disease but is most commonly associated with pulmonary stenosis or septal defects.\textsuperscript{159} NCM has also been associated with aneuploidies (Turner syndrome or trisomy 21, 18, and 13), copy number variations (22q11 deletion and 1p36 deletion), neuromuscular disease (Duchenne, Becker, limb-girdle, and multimicore), and other genetic syndromes (Soto, Marfan, and the RASopathies).

**Clinical Concepts in NCM**

Despite its designation as a separate cardiomyopathy by the American Heart Association in 2006,\textsuperscript{160} the definition of NCM remains controversial. The debate focuses on whether it is a distinct cardiomyopathy or a description of a morphological feature of other cardiomyopathies,\textsuperscript{161} as well as whether different causes represent unique diagnoses with different characteristics and outcomes. Current evidence suggests that NCM can be a manifestation of a developmental abnormality or secondary to other diseases.

Data support NCM as a manifestation of premature arrest of myocardial development during embryogenesis. Before the coronary arteries develop, the myocardium is trabeculated, which regresses once the coronary arteries form between weeks 5 and 8 of embryogenesis. The premature arrest of this final stage of cardiac morphogenesis leads to incomplete myocardial compaction with persistence of ventricular trabeculations and deep intertrabecular recesses, which may adversely affect subendocardial perfusion.\textsuperscript{162} Subendocardial ischemia increases fibrous and elastic tissue on the endocardial surface, contributing to the clinical phenotype of NCM.\textsuperscript{163}

**Presentation**

The clinical phenotype of NCM in children ranges from a benign to a severe course with progressive systolic or diastolic dysfunction, life-threatening arrhythmias, or thromboembolism. In the largest pediatric NCM study, nearly 40% of patients were infants, and 25% had a family history of cardiomyopathy. The signs and symptoms at presentation were heart failure (25%), suspected arrhythmia (17%), or murmur (18%).\textsuperscript{164} Electrocardiograms were abnormal in nearly all patients, with 8% displaying preexcitation. A third of patients had a documented tachyarrhythmia, including ventricular tachycardia (17%), atrial tachycardia (6%), and reentrant supraventricular tachycardia (8%). Patients with NCM and Barth syndrome have associated skeletal myopathy, neutropenia, prepubertal growth delay, and cardiomyopathy.\textsuperscript{165,166}

NCM is associated with an undulating phenotype characterized by transient improvements and declines in systolic function. NCM is commonly a component of a mixed phenotype: HCM/DCM (28%), HCM (27%), and DCM (19%), with more than half of patients presenting with systolic dysfunction and the eventual development of systolic dysfunction in an additional subset.\textsuperscript{164}

**Outcomes and Risk Prediction**

Children with NCM who have normal cardiac dimensions and normal systolic function are at very low risk for an adverse outcome. These findings are in contrast to outcomes in adults with NCM in whom heart failure and ventricular arrhythmia are frequent, and outcomes are poor.\textsuperscript{167} Children with an NCM and a mixed or dilated phenotype have a worse prognosis with an incidence of death or transplantation (18%–25%) that is higher in infants or those with congenital heart disease. Thus, differentiating the NCM subtype has important prognostic implications.\textsuperscript{20,164} Systolic dysfunction has been associated with an increased risk of arrhythmia, and arrhythmia independent of systolic dysfunction is a separate risk factor for sudden death. The mechanisms for arrhythmia remain unclear, with studies suggesting that progressive subendocardial ischemia and arrest of fetal myocardial development contribute to arrhythmogenesis.\textsuperscript{164} The majority of NCM patients who have undergone heart transplantation are pediatric with an average age of 3 years.\textsuperscript{168}

**Medical Management**

Approaches to the diagnosis and management of pediatric NCM are variable. The lack of consensus on diagnostic criteria leads to under- and overdiagnosis of the phenotype and limits understanding of the natural history of the disease. Single-center and multicenter data provide a basis for evaluating children with NCM but often focus on isolated NCM. Given these data, many centers evaluate children annually with noninvasive imaging (echocardiography or cardiac magnetic resonance imaging), electrocardiography, and ambulatory Holter monitoring. For older children who can comply, stress testing may also screen for exercise-induced arrhythmias. For those children with concomitant phenotypes, such as NCM/DCM or NCM/HCM, evaluation is typically more frequent, with many centers evaluating patients every 6 months or more often if symptoms change.

Thromboembolic disease in association with NCM occurs in ≤24% of adults.\textsuperscript{167} Many centers treat adults with antplatelet therapy or systemic anticoagulation, especially those with a history of systolic dysfunction. No data have been reported about the risk or occurrence of thromboembolic disease in pediatric NCM. Whether the risk profile for stroke is different in children is unclear and is a needed area of study given the potential impact of under- or overtreatment with anticoagulants on morbidity and mortality. The ability to identify patients at risk of sudden cardiac death remains limited, and there are no specific risk scores for pediatric NCM. The risks and benefits of AICD use must be weighed against the potential risk of sudden arrest. A better understanding of appropriate medical therapies is needed to assess efficacy. Preliminary data suggest that conventional remodeling therapies may be effective in NCM with a concomitant DCM phenotype, but larger studies are needed in the setting of mixed NCM disease.\textsuperscript{169}

**Disease-Specific Therapies in NCM**

Tafazzin is an acyltransferase responsible for acylation of cardiolipin, the major phospholipid of the mitochondrial membrane. TAZ deficiency impairs mature cardiolipin production and mitochondrial function and has substantial downstream effects on sarcomere assembly and myocardial contraction.
TAZ deficiency destabilizes mitochondrial respiratory chain complexes and affects supercomplex assembly. Changes in cardiac proteome have been identified and measured in TAZ knockdown mouse models of human Barth syndrome. The ability to generate induced pluripotent stem cell-cardiomyocyte models from individuals with Barth syndrome is an important development that may speed the assessment of potential therapies to correct the metabolic phenotype of the disease.

Future Research Directions

Several large longitudinal registries have provided invaluable data characterizing the epidemiology and outcomes of pediatric cardiomyopathies over the past 2 decades. Pediatric cardiomyopathies have a significant burden of disease in the affected population, and more precise biomarkers are needed to distinguish patients at risk who would benefit from invasive therapies such as AICD, mechanical assist, or transplantation from those who will remain clinically well or even improve over time. The increasing application of genomic analysis to the pediatric cardiomyopathy population is creating a wealth of information that requires expanded registry participation to further understanding of the pathogenic mechanisms underlying pediatric cardiomyopathies and the genetic, environmental, and other, as of yet undiscovered, modifying factors that impact the severity of disease. Clinical trials evaluating adult heart failure therapies in children are desperately needed to establish their safety and efficacy because there is evidence that the pathophysiology of heart failure and arrhythmias in the pediatric cardiomyopathy population differs from adults. Disease-specific therapies based on the underlying pathophysiology and genetics hold promise for the future.

Acknowledgments

We thank the Children’s Cardiomyopathy Foundation for its ongoing and consistent support for the work of the Pediatric Cardiomyopathy Registry.

Sources of Funding

This work was supported by grants from the National Heart, Lung, and Blood Institute NHLBI HL 53392 and the Children’s Cardiomyopathy Foundation. This work was supported by grants from the National Heart, Lung, and Blood Institute NHLBI HL 53392 and the Children’s Cardiomyopathy Foundation.

Disclosures

None.

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Tissue Doppler imaging consistently detects myocardial abnormalities in patients with hypertrophic cardiomyopathy and provides a novel means for an early diagnosis before overt hypertrophy.


Pediatric Cardiomyopathies
Teresa M. Lee, Daphne T. Hsu, Paul Kantor, Jeffrey A. Towbin, Stephanie M. Ware, Steven D. Colan, Wendy K. Chung, John L. Jefferies, Joseph W. Rossano, Chesney D. Castleberry, Linda J. Addonizio, Ashwin K. Lal, Jacqueline M. Lamour, Erin M. Miller, Philip T. Thrush, Jason D. Czachor, Hiedy Razoky, Ashley Hill and Steven E. Lipshultz

Circ Res. 2017;121:855-873
doi: 10.1161/CIRCRESAHA.116.309386
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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