Hypertrophic cardiomyopathy (HCM) is a genetically diverse disorder affecting the hearts of both children and adults. Regardless of its etiology, inappropriate ventricular hypertrophy is the key phenotypic finding of the disease. HCM often occurs in families, with an identifiable inheritance pattern, but many sporadic cases are also identified. Recent data classify two-thirds of children as having idiopathic disease. HCM is often diagnosed in the setting of a broader genetic syndrome (Friedreich's ataxia, Noonan syndrome, etc.), or can be found in otherwise healthy individuals (i.e., familial isolated cardiomyopathy). An increasing number of sarcomeric mutations have been discovered as causative factors, often showing a dominant inheritance pattern within affected families. Other primary causes of HCM are varied and include inborn errors of metabolism, malformation syndromes, and neuromuscular disorders.

HCM causes significant morbidity and mortality in patients of all ages and is a leading cause of unexpected sudden death in previously well children. It is a relatively rare and diverse disease where, especially in the pediatric age group, a variety of etiologies and often contradictory outcomes have been described.

Due to disease diversity, outcome diversity, and a limited number of patients to study, information regarding HCM is incomplete. Treatment strategies of childhood HCM are generally drawn from adult management experience or professional consensus. The uncertainty regarding pediatric HCM leads to ethical challenges when caring for a child with this disease. This article reviews the latest information available on HCM, including recent epidemiological and cause-specific outcome data derived from the Pediatric Cardiomyopathy Registry (PCMR). Potential future diagnostic and treatment options will also be addressed.

Diagnosis

HCM may be clinically suspected by a number of non-specific findings on the basis of history (e.g., chest pain/pressure, shortness of breath, fatigue, syncope, palpitations) or physical examination (development of a new heart murmur). Family history may be suggestive if positive for known disease or early unexpected death. However, it has been found that only 10% of patients with newly identified HCM are diagnosed on the basis of history and physical examination alone. The addition of an electrocardiogram (ECG) adds greatly to the evaluation, as the majority (at least 75–80%) of patients will show hypertrophy or T-wave abnormalities that can then prompt further cardiac evaluation. The presence of HCM is best confirmed with 2D echocardiography (2D ECHO), which easily demonstrates characteristic ventricular changes.

Once a child is diagnosed with HCM, a specific disease etiology is often sought. This evaluation is often influenced by the age of the child at the time of diagnosis and may include metabolic studies, endomyocardial biopsy, or chromosomal analyses. Studies reveal that metabolic testing of blood and urine may be the most productive investigation for establishing a specific diagnosis in the vast majority of patients with HCM. Although not widely used, skeletal muscle biopsy may be helpful for some patients with HCM suspected of having a mitochondrial disorder. Surveys indicate that currently available testing is underutilized and that increased testing might identify a specific etiology in a greater proportion of these children. Overall, identifying these variables may ultimately lead to a better understanding of the HCM disease process and, hopefully, allow for etiology-specific and more successful treatment of this challenging disorder.

Epidemiology and Etiology

The PCMR is the principal database of sociodemographic and clinical information on children diagnosed with cardiomyopathy across the US and
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Canada. It was founded in 1994 by the National Heart, Lung, and Blood Institute (NHLBI) and consists of both a prospective and a retrospective data set. The retrospectively collected data were obtained on children diagnosed with all types of cardiomyopathy between 1990 and 1995 and allowed for detailed study of the causes and the natural history of the disease. Prospectively collected data have followed children diagnosed with cardiomyopathy since 1996 in two specific regions of the US (New England and the Central Southwest). These data have permitted a detailed analysis of the epidemiological features of childhood cardiomyopathy.7

The PCMR has estimated the overall incidence of pediatric cardiomyopathy (combined dilated, restrictive, and hypertrophic types) at 1.13 cases per 100,000 children. HCM represents nearly half of these cases, with an incidence of 0.47 cases per 100,000 children. These data are consistent with similar findings in Finnish and Australian populations.8,9 HCM is diagnosed more frequently in males, blacks, and infants less than one year of age.7

In a retrospective PCMR cohort of 916 patients with all types of cardiomyopathy, 313 were diagnosed with HCM. Only 112 children had a known etiology of their disease. These included 27.7% with familial isolated cardiomyopathy, 23.2% with a neuromuscular disorder (most commonly Friedreich's ataxia), 26.8% with an inborn error of metabolism (most commonly Pompe disease), and 22.3% with a malformation syndrome (most commonly Noonan syndrome).7 Children with a known cause of HCM were more likely to be female and be small for their age, as evidenced by a lower mean height-for-age and a lower mean weight-for-age score. They were also more likely to present with symptoms of congestive heart failure (CHF) and to have an inborn error of metabolism. Those patients who were found to have increased left ventricular (LV) posterior wall thickness without outflow tract obstruction on diagnosis were more likely to have a known cause of HCM; these were predominantly patients with a variety of mitochondrial and other metabolic disorders (especially Pompe disease) and Friedreich's ataxia.2

Genotyping is now available for sarcomeric protein genes for HCM with over 600 individual mutations identified for HCM. The prevalence of unexplained LV hypertrophy is about 1:500 healthy adults in the US, with about 60% having sarcomeric gene mutations.

Testing allows pre-clinical identification of individuals at risk and has implications for disease in the molecular era. There are many undiscovered gene modifiers in genotyped children with HCM who are either positive or negative for mutations. In addition, about 15–20% of

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In the same cohort, family history of cardiomyopathy predicted a significantly higher rate of causal diagnoses for all cardiomyopathy types. Family histories of a genetic syndrome and sudden death were predictive of a causal diagnosis for HCM.7 Patients with inborn errors of metabolism and malformation syndromes are diagnosed with HCM earlier than patients with neuromuscular disorders or familial isolated cardiomyopathy, and those with neuromuscular disorders are diagnosed later than those with isolated HCM.1

Genotyping analysis of affected individuals is beginning to become a more widespread endeavor. Although specific mutations are not always found, they allow for specific screening of other family members and may ultimately influence patient management decision-making. Genotyping is now available for sarcomeric genes. There are 11 sarcomeric protein genes for HCM with over 600 individual mutations identified for HCM. The prevalence of unexplained LV hypertrophy is about 1:500 healthy adults in the US, with about 60% having sarcomeric gene mutations.

Testing allows pre-clinical identification of individuals at risk and has implications for disease in the molecular era. There are many undiscovered gene modifiers in genotyped children with HCM who are either positive or negative for mutations. In addition, about 15–20% of children with HCM mutations have double mutations, known as compound heterozygosity. Testing differentiates HCM from other phenocopies and from ‘athlete's heart.’ In addition, it provides a definitive diagnosis independent of age and clinical features. Molecular characterization provides insights into disease mechanisms, including the common mutations in children, triggers of contractile dysfunction and symptoms, the drive for pathological cardiac remodeling, and potential therapeutic targets. Molecular characterization is likely to improve treatment strategies from palliation of symptoms to disease modification and prevention. Molecular characterization may answer the question of whether early biochemical changes precede functional and morphological changes. In addition, it may tell us whether altering biochemistry can modify the phenotype. Lastly, it may be able to establish manifestations of HCM that can be reversed.

Genotyping for HCM is now commercially available and, with increasing cost-effectiveness, most insurance companies now cover this type of testing. Gene testing is rapidly becoming a standard of care practice, with increasing evidence of benefit in terms of predicting outcome measures and improving family screening, and may lead to potential future treatment options.7

**Outcomes**

Outcome prediction is very difficult for individual children with HCM. Patients may develop progressive exercise intolerance and arrhythmias and have a background risk for sudden cardiac death (SCD). Many patients with milder hypertrophy may remain entirely asymptomatic. Risk factors for SCD have been identified for familial HCM in adults. These include a history of prior cardiac arrest, family history of sudden death, spontaneous sustained ventricular tachycardia, exercise-induced hypotension, syncope, and some high-risk genotypes.7 In addition, high degrees of LV outflow obstruction have been linked to both SCD and symptom progression. However, these risk factors are not well verified in children, adding to the difficulty of outcome predictability.
Cardiology

Data from the PCMR clearly show the impact of age at diagnosis on outcome. Mortality is higher in children diagnosed during infancy, although the outcome in children surviving beyond the first year becomes the same as that in children diagnosed later in life. Overall, patients with idiopathic HCM over one year of age, regardless of age at diagnosis, were found to have an annual mortality rate of 1%, a rate lower than previously reported and not much different from the mortality rate found in adult-based studies. In relation to etiology, children with an inborn error of metabolism or a malformation syndrome have the worst outcome. Poorer outcomes also occur in combined forms of HCM (those with a dilated or restrictive component). Other factors associated with poorer prognosis include increased LV posterior wall thickness, increased LV diastolic diameter, decreased fractional shortening, and the presence of CHF at diagnosis. 10

Future of Hypertrophic Cardiomyopathy in Childhood

Many questions remain as to the best practice standards when confronting pediatric HCM. HCM remains the most common cause of SCD in children, making risk stratification a central clinical concern. A detailed patient and family history with particular attention to syncope and sudden death should be obtained during the initial patient evaluation. Generally accepted guidelines mandate activity restrictions once the diagnosis of HCM is made, as sudden arrhythmic deaths typically occur during exercise. Beta-adrenergic blockade or calcium channel blockers can be used to decrease outflow tract obstruction and improve exercise tolerance. However, the risk for SCD persists, imparting significant stress on these children and families.

In the adult experience, prophylactic implantable cardioverter-defibrillator (ICD) placement has been shown to be an effective intervention that prolongs the life of those affected with HCM. 11 ICD placement is a relatively invasive and expensive endeavor not without its complications, especially in smaller pediatric patients. Risk stratification and patient selection therefore remain key issues faced daily by pediatric cardiologists. In general, ICD implantation is recommended for patients with the previously mentioned risk factors (i.e. documented ventricular tachycardia, history of syncope, abnormal exercise hemodynamics, and severe outflow tract obstruction). However, adult standards for ICD placement may not apply directly to children, and most cardiologists can report at least anecdotal experience of losing a ‘low-risk’ patient to a sudden and lethal arrhythmia. Precisely defining pediatric ICD implantation criteria is certainly desirable, but doing so via clinical trials may be a challenge. For example, a randomized trial of ICDs in children would be hindered by the slow pace at which patients achieve hard end-points, the absence of validated surrogate end-points, and a potential lack of consensus in the clinical community. Some clinicians may be hesitant to withhold ICD placement in such a ‘high stakes’ setting.

Comprehensive, multidisciplinary treatment programs are well known for improving health outcomes and reducing costs in adult heart failure and some specific pediatric chronic diseases. Regrettably, very few such programs exist for children with heart failure, and these programs have not been formally evaluated or described in the literature. Comprehensive, multidisciplinary heart failure programs could be the next step forward in improving the management of HCM. 12

As the genetic and molecular bases of HCM become more defined, we may be able to risk-stratify based on specific genotype testing. The link between etiology and outcome indicates that when a diagnosis of HCM is made, determination of the etiology should be a primary goal. It is likely that some children with mild hypertrophy and a specific ‘low-risk’ genotype could be cleared of activity restrictions, and fears of SCD could be alleviated. Conversely, patients with high-risk genotypes would then be specifically and appropriately offered aggressive medical and device therapy. As suggested by Colan, the creation of a repository providing information about specific laboratories and tests may facilitate the pursuit of etiological diagnosis. 13 Genotyping should become part of routine testing, helping to identify index patients and screen family members; its systematic use will provide information about the type and frequency of mutations occurring in children. A recent genotype study identifying some of the specific gene mutations responsible for childhood and adult HCM has moved us closer to this paradigm of gene-based diagnosis and management. Of course, the ultimate goal will be a molecular cure for HCM with the future promise of gene therapy interventions. 14

The use of magnetic resonance imaging (MRI) to evaluate the degree of myocardial fibrosis in patients with HCM appears to be an additional promising tool to identify patients at risk for sudden death, but at the present time there are insufficient data available to confirm this. 15

Despite the known limitations of utilizing registry data for proposing novel treatments, well-designed clinical registries for rare diseases can provide valuable management and treatment data for children with HCM. 16 Longitudinal studies, such as the PCMR, remain a key element in collecting information in relation to etiology, diagnosis, treatment, and outcomes, and thus advance our understanding of disease.