Pediatric dilated cardiomyopathy (DCM) carries substantial morbidity and mortality and costs US society annually a substantial portion of the estimated $2 billion associated with pediatric heart failure.1–3 Among children after the first year of life, DCM is the most common indication for cardiac transplantation.1,2 Common unfavorable outcomes of DCM are death, usually resulting from congestive heart failure (CHF) or sudden cardiac death, and cardiac transplantation. Transplantation is commonly combined with death as a poor outcome because it is assumed to be performed in children who would otherwise be at high risk of short-term death. However, transplantation has its own negative consequences: a lifetime of immunosuppressive therapy, potential retransplantation, associated comorbidities, and increased risk of premature death.2,4 Two population-based studies, including the Pediatric Cardiomyopathy Registry (PCMR), reported freedom from death and transplantation at 1 year to be 72% and 69% and at 5 years to be 63% and 54%.4,5 These survival rates from the time of DCM diagnosis are similar to what they were decades ago.1 Median life expectancy after
transplantation is only between 10 and 15 years, although younger children and children receiving more recent transplantations have been observed to have better outcomes.\(^1\) Therefore, better identification of children with DCM at high risk for death would avoid unnecessarily exposing them to the risks of potentially poor outcomes after transplantation while ensuring that children who are truly at imminent risk for death receive life-saving surgery. We sought to determine whether the risk factors for death in children with DCM are the same as those used in practice to determine transplantation or whether other unrecognized risk factors for death are not being weighted sufficiently in the transplantation decision.

**Clinical Perspective on p 823**

Prior analyses from the PCMR\(^5\) and a systematic review of studies of risk factors for the composite end point of death or transplantation in children with DCM at the time of diagnosis have implicated older age, worse left ventricular (LV) fractional shortening (FS) and ejection fraction, and CHF as significant predictors.\(^6\) Our present analyses use competing risk methods to separate the effects of these risk factors according to their impact on death and transplantation. The analyses are stratified by the etiology of DCM at the time of diagnosis to simulate the real-world considerations that affect optimal medical management or referral for transplantation.

**Methods**

The Pediatric Cardiomyopathy Registry

The PCMR is a central repository of information on pediatric cardiomyopathy across North American clinical centers.\(^2\) Briefly, children (<18 years of age) diagnosed with DCM by a pediatric cardiologist were identified by chart review and enrolled into 2 cohorts. The retrospective cohort consists of children at 39 tertiary care centers diagnosed between January 1, 1990, and December 31, 1995. The prospective cohort consists of children at 98 pediatric cardiac centers diagnosed after January 1, 1996. The method of data collection was the same (see below). Although the retrospective cohort (n=1214, 72%) compared with the prospective cohort (n=468, 28%) has longer median follow-up time (1.9 versus 1.1 years; \(P<0.001\), the outcomes for the 2 cohorts are similar.\(^3\)

Enrollment required echocardiographic evidence of LV dilation and systolic dysfunction, semiquantitative echocardiographic patterns, diagnostic endomyocardial biopsy results, or other compelling clinical evidence.\(^3\) Fourteen criteria excluded secondary cardiomyopathies (ie, toxic exposures, endocrine disorders, immunologic diseases). For both the retrospective and prospective cohorts, data were collected from the time of diagnosis and annually thereafter through medical record review using standardized case report forms and trained data collectors. Subjects were followed up until death, heart transplantation, or transfer to a nonparticipating institution or until they were lost to follow-up. This report is based on the PCMR database as of January 3, 2008. All participating PCMR centers obtained institutional review board approval.

This study was limited to children who were recorded as having “pure” DCM at the time of diagnosis (ie, excluding mixed hypertrophic or restrictive phenotypes). The cases were further classified into 6 etiologic groups at baseline based on the PCMR typology\(^5,8\) and on published guidelines: \(^2\) inborn errors of metabolism, malformation syndrome, neuromuscular disease (NMD), familial isolated cardiomyopathy, myocarditis, and idiopathic DCM.

**Study Variables**

Demographic variables included age, height, weight, and race, with height and weight normalized to \(z\) scores according to Centers for Disease Control and Prevention standards. Clinical information included etiology as per the PCMR algorithm and familial history of various related diseases and outcomes. Echocardiographic variables, including LV end-diastolic dimension (EDD), posterior wall thickness, septal thickness, and mass, were expressed as \(z\) scores conditional on body surface area; LVFS was expressed as a \(z\) score conditional on age.\(^10,11\)

**Statistical Methods**

Descriptive data are presented for all children stratified by etiology as percentages or means and SDs; skewed continuous data are summarized as medians and quartiles. Children with incomplete baseline data were included in all analyses for which they could contribute data. However, multivariate analyses were limited to those children with complete baseline data for all candidate covariates being considered in the stepwise selection. The 2 primary outcomes were time to death and time to transplantation, with censoring occurring when a child was lost to follow-up. Survival and transplantation figures and estimates were calculated from the cumulative incidence of competing risks from the time of DCM diagnosis.\(^12\) The Cox proportional hazards regression analysis, modified for competing risks, identified both univariate and multivariate predictors of outcomes for each etiology.\(^12,13\) In competing risks analysis, each predictor in the Cox regression model generated 2 effect estimates and 2 \(P\) values, one for the impact of the predictor on mortality and the other for the impact on transplantation. The competing risk model included an interaction term to determine whether the effect of the predictor on mortality differed from its effect on transplantation. If the interaction term was significant, 2 separate effects were estimated. If the interaction term was not significant, then it was removed and a single effect estimate and \(P\) value were presented, reflecting the common impact of the predictor on both outcomes.

Because of the large number of potential predictors being considered, the final multivariable model was developed in a 2-step process. Initially, we included only those predictors that were significant at \(P<0.05\) in stepwise analyses completed in groups of related variables (demographics, anthropometrics, clinical, and historical). Group winners were then used to build a model in a stepwise selection with significant variables selected at \(P<0.01\). All analyses were conducted with the Statistical Analysis System version 9.1 (SAS Institute Inc, Cary, NC) and an SAS macro for competing risks analysis.\(^12\)

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

**Demographics and Clinical Characteristics**

The sample consisted of 1731 children with DCM (Tables 1 and 2). Of these, 6 with malformation syndromes and 43 with inborn errors of metabolism were excluded because there were too few children for analysis of their respective etiology.

**Children With Idiopathic Disease**

The largest group had idiopathic DCM (n=1192, 69%); most were white (54%), male (50%), and infants (<1 year of age, 47%) at the time of diagnosis. Growth characteristics were below normal for age. Three quarters presented with symptoms of CHF. Echocardiographic measurements, recorded in 81%, revealed LV dilation, increased LV mass, and poor LV systolic function. Septal thickness and LV posterior wall thickness \(z\) scores were also below normal. A family history of associated conditions was present in 28%. For 157 (13%), an etiology was subsequently identified at some time after the first month of DCM diagnosis. The most common etiologies discovered were myocarditis (n=86), inborn errors of metab-
olism (n=31), and familial isolated cardiomyopathy (n=25); 15 had other causes. However, the initial diagnosis of idiopathic was used for all subsequent analyses because the average time between diagnosis and death or transplant was only a few months.

**Children With Neuromuscular Disease**
Of the 139 children with NMD, 84% (n=117) had Duchenne and 8% (n=11) had Becker muscular dystrophy. Most were male (96%) and white (72%). All presented with cardiomyopathy after 6 years of age; 83% presented after 12 years of age. Only 39 (28%) had symptoms of CHF at diagnosis. Half had a family history of an associated condition, most commonly a genetic syndrome (32 of 74, 42%) or cardiomyopathy (12 of 58, 20%).

**Children With Familial Isolated Cardiomyopathy**
Most of the 79 children (72, 91%) with familial isolated cardiomyopathy were believed to have an autosomal dominant inheritance pattern. They were older at diagnosis compared with those with idiopathic DCM or myocarditis (median age, 6 years), and 56% had CHF. This group had the greatest proportion of a family history of sudden deaths (53%).

**Children With Myocarditis**
Of the 272 children with myocarditis, 112 (41%) met the Dallas pathology criteria\(^1\); the others were classified as probable cases. They had baseline characteristics similar to those of the idiopathic group, although more presented with CHF (83% versus 75%; \(P<0.01\)).

**Outcomes**
The median follow-up time for the entire sample was 1.3 years (interquartile range, 0.2 to 4.0 years), and for those who were alive at the last follow-up and not transplanted, the median follow-up time was 2.8 years (interquartile range, 0.9 to 5.5 years). Overall, 665 children (38%) experienced either death or transplantation, with the majority (512, 77%) undergoing transplantation. Among patients listed for transplantation, the median time from diagnosis to listing for transplantation was 1.4 months; however, 22% who were listed (n=112) did not receive a transplant, and of those, 41% (n=46) died.

Among the 1192 children with idiopathic DCM, 487 had an event, of whom 161 (33%) died and 326 (67%) received a transplant. As Table 3 and the Figure, A, show, in this cohort at 1 year after diagnosis, the probability of death was 11%, the probability of transplantation was 24%, and the remaining 66% of children were alive and transplant free. By 5 years, the probability of death had increased to 16% and the probability of transplantation had reached 33%, whereas the percentage alive and transplant free had decreased to 51%. The idiopathic DCM group had the largest proportion of deaths among those listed and awaiting transplantation.

Of the 139 children with neuromuscular DCM, 56 had a poor outcome. The outcomes were primarily deaths (47, 84%), whereas only 9 received a heart transplant; of these 9, most (n=5) had Becker muscular dystrophy and none had Duchenne muscular dystrophy. At 1 year, the probability of death was 8%, the probability of transplantation was 6%, and the remaining 87% of children were alive and transplant free.
The results of multivariate modeling of risk factors for death or transplantation for each etiology are shown in Table 4. For children with idiopathic DCM, older age, depressed LVFS, and the presence of CHF independently predicted both death and transplantation. Lower height-for-age was associated with an increased risk of death but not of transplantation. In contrast, higher LVEDD was associated with an increased risk of transplantation but a decreased risk of death. In fact, among the children who have not been transplanted, an elevated LVEDD is associated with decreased, not increased, mortality.

For children with neuromuscular DCM, the final competing risks multivariate model included LVFS and LVEDD; an interaction with outcome was present for the latter. As was seen for children with idiopathic DCM, depressed LVFS was significantly and equally associated with both death and transplantation. Left ventricular EDD also showed a similar result, with elevated LVEDD strongly associated with increased transplantation but only weakly and nonsignificantly associated with death.

In the myocarditis group, the multivariate model showed that increased age, CHF, and increased LVEDD at presentation were associated similarly with both death and transplantation. For familial isolated cardiomyopathy, although several factors were associated with increased risk of either death or...
transplantation in univariate analyses (CHF, increased LVEDD, worse LVFS, LV end-diastolic septal thickness, or weight-for-height), a multivariate model with independently significant factors could not be fitted. However, the best model is presented (Table 4) after the exclusion of those with significant collinearity or missing data.

**Discussion**

Compared with the initial PCMR report on the incidence of pediatric DCM and its outcomes, this study assessed the differential effects of demographic and clinical factors determined at the time of DCM diagnosis on the subsequent risk of death or transplantation for each etiology. Using a competing risks analytic model, we identified novel differential risk factors for death and transplantation. Identifying these differences may improve the initial assessment, treatment, and survival of children with DCM.

Previous studies differ on the effect of age at diagnosis on mortality in children with DCM. In idiopathic DCM, we found that age at diagnosis of ≥6 years was associated with a 3- to 4-times increased risk of death or transplantation compared with infants. The effect of age in children with myocarditis also showed an association with older age and death or transplantation; however, it was best explained as a direct linear association between the outcomes and age at diagnosis. At presentation, in idiopathic DCM, older children may have more deleterious disease, perhaps because myocardial damage has had more time to occur or, conversely, in myocarditis, the younger heart has more reserve. The cumulative, long-term effects of this smoldering disease may diminish the reserve in a maturing heart, ultimately making recovery from structural and functional problems less likely, as opposed to a specific insult in those with myocarditis, whose age effect reflects reserve. The fact that age was not predictive of death or transplantation in the NMD group is not surprising because children are generally diagnosed with DCM at a much later age, usually during adolescence.

Congestive heart failure present when DCM is diagnosed is the single strongest predictor of death or transplantation for idiopathic DCM and myocarditis but not in patients with NMD. In our population, only 29% of children with NMD had CHF at the time of DCM diagnosis compared with >50% for all other etiologies, which is not surprising because a large proportion of this population is prospectively screened by echocardiography and DCM is captured before overt symptomatic CHF. The mortality rate was much greater than the transplantation rate for this group, likely indicative of the fact that the presence of respiratory compromise in children with NMD makes them less suitable for transplantation than children with other etiologies of DCM. For those with idiopathic DCM and myocarditis, the severity of symptoms is associated with death, and the decision to perform a cardiac transplantation reflects the practice patterns of pediatric cardiologists using appropriate management.

The absence of LVFS as a predictor of death or transplantation for children with DCM caused by myocarditis may be explained by the temporal process of the disease and time-dependent effects of circulating proinflammatory cytokines (eg, tumor necrosis factor and interleukin-6). Cytokine release is hypothesized to affect LV systolic function adversely. The decrease in LVFS would be evident early in the course of most children with myocarditis, but this is not necessarily true for children with NMD and idiopathic DCM. As demonstrated, children with preexistent cardiac structural damage, ie, the idiopathic and NMD groups, who have a decrease in LVFS at the time of diagnosis appear to have worse outcomes. In these groups, the decreased LVFS and its continued deterioration could possibly relate to a chronic inflammatory response, but the outcome appears to be different than in isolated myocarditis, which represents an acute process that usually resolves on its own. The hypothesized role of chronic cytokine release is supported by nonrandomized studies of antiinflammatory agents such as intravenous immunoglobulin or steroids that have reported some benefit in small case series of children with DCM, as well as in a larger Italian cohort with 13 years of follow-up. We have seen similar findings in children with HIV and LV dysfunction treated with immunoglobulins. Additionally, equivocal findings in trials of adults and a Cochrane review support the argument that transient (as opposed to chronic) inflammation may explain the particular constellation of predictors uncovered by this analysis.

Nevertheless, some children with myocarditis do quite poorly. Other theories have been put forth regarding myocarditis pathology to explain why these children do not fully recover, including the cleavage of myocardial structural proteins like dystrophin by viral proteases and the persistence of coxsackievirus B in the myocardium, leading to a low-grade, noncytolytic, chronic infection in the heart. Either theory may explain worse outcomes with longer follow-up time but with structural damage as its mechanism.
Higher LVEDD $z$ scores predicted a significantly greater risk of either death or cardiac transplantation among children with myocarditis, a greater risk of transplantation but a greater likelihood of survival in children with idiopathic DCM, and a greater risk of transplantation but not death in children with NMD. Although LV dilation is expected by definition in all children with DCM, greater LV dilation appeared to be a significant factor in the decision to perform transplantation in those with idiopathic DCM and NMD. For example, in children with idiopathic DCM, the median LVEDD $z$ score was 5.7 among children who were listed for transplantation but only 4.3 in children who were not listed ($P<0.001$). However, the role of elevated LVEDD in mortality risk is less clear. It is possible that the children with the
highest levels of LVEDD were appropriately triaged to transplantation, but it is impossible to examine this empirically because we cannot know what would have happened to these children if the transplantation had not occurred. We do know, however, that among 69 children who were listed but not transplanted, the median LVEDD $z$ score was 5.8 in children who were still alive at the last follow-up but only 5.2 in those who died (and 5.7 in the children who were transplanted). There is at least the possibility that although elevated LVEDD is bad, there are other risk factors that, when present, are even worse.

Another explanation may be that comparatively greater LVEDD is a surrogate for children with worse symptoms and reflects the listing practices based on that criterion. In comparison, an associated study evaluating echocardiograms performed within 6 months of listing has linked greater
LVEDD to increased mortality both during the postlisting period and within 6 months after transplantation in children with DCM. A stronger effect was noted in those <5 years of age at the time of diagnosis.23 Once the decision is made to transplant a simple criterion that does not appear to factor into the transplant listing process as frequently as it should.

Several limitations should be considered in the evaluation of this analysis. Children in the PCMR may have more severe disease because all were identified as part of a clinical interaction with a healthcare provider, not as part of asymptomatic screening. Although the PCMR has the largest reported population of children with DCM, the power to detect statistically significant differences in risk factors for death versus transplantation is limited by the small sample size for certain etiologic subgroups. For example, data from the registry likely underestimate the true proportion of familial cases because not all families were thoroughly evaluated for the presence of cardiac disease.

Limitations
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Table 4. Results of Multivariate Modeling of Competing Risks of Death and Heart Transplantation by Etiology

<table>
<thead>
<tr>
<th>Factor at Diagnosis</th>
<th>Combined (Death or Transplantation)</th>
<th>Death</th>
<th>Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic DCM (n=536)</td>
<td></td>
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<td></td>
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<tr>
<td>Age at diagnosis</td>
<td></td>
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<tr>
<td>1 to &lt;6 y vs infants (&lt;1 y)</td>
<td>1.20 (0.76–1.98) [0.5]</td>
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<tr>
<td>6 to &lt;12 y vs infants (&lt;1 y)</td>
<td>4.22 (2.83–6.61) [&lt;0.001]</td>
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<tr>
<td>12 to &lt;18 y vs infants (&lt;1 y)</td>
<td>3.52 (2.37–5.23) [&lt;0.001]</td>
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<tr>
<td>CHF (present vs absent)</td>
<td>3.48 (2.24–5.41) [&lt;0.001]</td>
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<tr>
<td>LVEDD z score (per 1-SD increase)</td>
<td>0.87 (0.77–0.98) [0.019]</td>
<td>1.11 (1.02–1.21) [0.02]</td>
<td></td>
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<tr>
<td>LVFS z score (per 1-SD increase)</td>
<td>0.86 (0.8–0.91) [&lt;0.001]</td>
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<tr>
<td>Height-for-age z score (per 1-SD increase)</td>
<td>0.77 (0.67–0.9) [&lt;0.001]</td>
<td>0.99 (0.89–1.1) [0.69]</td>
<td></td>
</tr>
<tr>
<td>Neuroromuscular disease (n=98)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDD z score (per 1-SD increase)</td>
<td>1.23 (0.96–1.59) [0.1]</td>
<td>3.45 (1.74–6.84) [&lt;0.001]</td>
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</tr>
<tr>
<td>LVFS z score (per 1-SD increase)</td>
<td>0.85 (0.74–0.97)</td>
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<td></td>
</tr>
<tr>
<td>Myocarditis (n=212)</td>
<td></td>
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<tr>
<td>Age (per 1-y increase)</td>
<td>1.10 (1.05–1.16) [&lt;0.001]</td>
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<tr>
<td>CHF (present vs absent)</td>
<td>5.51 (1.32–23) [0.02]</td>
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<tr>
<td>LVEDD z score (per 1-SD increase)</td>
<td>1.20 (1.06–1.36) [0.005]</td>
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<tr>
<td>Familial isolated DCM (n=64)</td>
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<tr>
<td>CHF (present vs absent)</td>
<td>2.22 (0.45–11) [0.33]</td>
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<tr>
<td>LVFS z score (per 1-SD increase)</td>
<td>0.85 (0.68–1.07) [0.17]</td>
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</table>

CI indicates confidence interval; DCM, dilated cardiomyopathy; CHF, congestive heart failure; LV, left ventricular; EDD, end-diastolic dimension; and FS, fractional shortening.

*Adjusted for subgroup (Duchenne, Becker, or other).
Lastly, the relatively short follow-up period limits the ability to extrapolate our results. However, given that the majority of events occur within the first year after diagnosis of DCM, our overall conclusions should be clinically applicable. Continued follow-up is warranted to establish more accurate predictors of long-term events.

Conclusions
Using competing risk analysis, we found that at the time of DCM diagnosis, the presence of CHF, echocardiographic evidence of more severe disease, and increased age at diagnosis predicted worse outcomes, with certain key differences between etiologies. For children with idiopathic disease, diagnosis after 6 years of age, CHF, decreased LVFS, increased LVEDD, and decreased height-for-age predicted worse outcomes. Increased LV dilation was predictive of cardiac transplantation but not mortality in idiopathic DCM, calling into question the importance of this factor in the decision to list a child for transplantation. Our analysis showed that children with idiopathic DCM and lower height-for-age z scores might be dying before consideration for listing or receipt of potentially beneficial heart transplantation, suggesting that impaired height should be an important consideration in the decision to list a child for transplantation. Whether height as a product of nutrition, growth, or disease can be modified earlier in the disease course to decrease the risk of death may be a new area of research. For children with NMD, decreased LVFS predicted death or transplantation, whereas increased LVEDD predicted transplantation but not death. For children with myocarditis, older age at diagnosis, CHF, and increased LVEDD predicted death or transplantation. These results suggest that the etiology of DCM modifies the importance of certain predictive factors. The ability to predict failed medical management may improve if the etiology of cardiomyopathy can be established earlier. Additionally, analyzing registry data in this manner allows the postulation of predictive algorithms of clinical outcomes.

Acknowledgments
We thank the participating clinical centers for patient recruitment.

Sources of Funding
This study was supported by National Heart Lung and Blood Institute (NHLBI) F31HL094100 (Dr Alvarez). The PCMR is supported by NHLBI R01HL53392 (Dr Lipshultz) and the Children’s Cardiomyopathy Foundation.

Disclosures
None.

References


**CLINICAL PERSPECTIVE**

Prior studies of outcomes for children with dilated cardiomyopathy (DCM) have used a composite end point of death and cardiac transplantation and may have missed identifying predictive factors differentially affecting outcomes, which affect the transplantation listing process. Using competing risk analysis, this study found that at the time of DCM diagnosis, the presence of congestive heart failure, echocardiographic evidence of more severe disease, and increased age at diagnosis predicted worse outcomes, with certain key differences between etiologic groups. For children with idiopathic disease, diagnosis after 6 years of age, congestive heart failure, decreased left ventricular (LV) fractional shortening, increased LV end-diastolic dimension, and decreased height-for-age predicted worse outcomes. Increased LV dilation was predictive of use of transplantation but not of mortality in idiopathic DCM, calling into question the importance of this factor in the decision to list for transplantation. Routine height measurement could highlight those with idiopathic DCM and lower height-for-age $z$ scores who might require more urgent consideration for transplantation listing. For children with neuromuscular disease, decreased LV fractional shortening predicted death or transplantation, whereas increased LV end-diastolic dimension predicted transplantation but not death. For children with myocarditis, older age at diagnosis, congestive heart failure, and increased LV end-diastolic dimension predicted death or transplantation. These results suggest that the etiology of DCM modifies the importance of particular predictive factors. The ability to predict failed medical management may improve if the etiology of the cardiomyopathy can be established earlier. Additionally, analyses of registry data in this manner allow the postulation of predictive algorithms of clinical outcomes.
Competing Risks for Death and Cardiac Transplantation in Children With Dilated Cardiomyopathy: Results From the Pediatric Cardiomyopathy Registry

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_Circulation_. 2011;124:814-823; originally published online July 25, 2011;
doi: 10.1161/CIRCULATIONAHA.110.973826

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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