# The impact of heart failure severity at time of listing for cardiac transplantation on survival in pediatric cardiomyopathy

Ranae L. Larsen, MD,[a] Charles E. Canter, MD,[b] David C. Naftel, PhD,[c]
Margaret Tressler, MPH,[c] David N. Rosenthal, MD,[d] Elizabeth D. Blume, MD,[e]
William T. Mahle, MD,[f] Delphine Yung, MD,[g] William R. Morrow, MD,[h]
E. John Orav, PhD,[e] James D. Wilkinson, MD,[i] Jeffrey A. Towbin, MD,[j] and
Stephen E. Lipshultz, MD[i]

From [a]Department of Pediatrics, Loma Linda University, Loma Linda, California; [b]Department of Pediatrics, Washington University, St. Louis, Missouri; [c]Department of Surgery, University of Alabama Birmingham, Birmingham, Alabama; [d]Department of Pediatrics, Stanford University, Palo Alto, California; [e]Department of Pediatrics, Department of Internal Medicine, Harvard University, Boston, Massachusetts; [f]Department of Pediatrics, Emory University, Atlanta, Georgia; [g]Department of Pediatrics, University of Washington, Seattle, Washington; [h]Department of Pediatrics, University of Arkansas, Little Rock, Arkansas; [i]Department of Pediatrics, University of Miami, Miami, Florida; and [j]Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio.

**KEYWORDS:**
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**BACKGROUND:** The survival benefit of heart transplantation in adult heart failure is greatest for the sickest patients and negligible for patients not requiring inotropic or mechanical support. We hypothesized a similar survival benefit of heart transplantation for childhood cardiomyopathies with heart failure.
**METHODS:** A merged data set of children registered in both the Pediatric Cardiomyopathy Registry and the Pediatric Heart Transplant Study was used to assess differences in mortality before and after transplant in patients with different levels of heart failure severity. Severity was scored 2 if mechanical ventilatory or circulatory support was required, 1 if intravenous inotropes were required, or 0 if no support was required.
**RESULTS:** For 332 eligible children, 12-month mortality after listing was 9% for those with a severity score of 0 ($n = 105$), 16% with a score of 1 ($n = 118$), and 26% with a score of 2 ($n = 109$; $p = 0.002$) with a 3%, 8%, and 20% mortality with severity scores at listing of 0, 1, and 2, respectively, occurring before transplant. Patients listed with a score of 0 frequently deteriorated: 50% received an allograft or died before transplant with severity scores of 1 or 2. The risk of deterioration increased with previous surgery (relative risk, 3.84; $p = 0.03$) in the short-term and with lower left ventricular mass $z$-score at time of presentation (relative risk, 1.74; $p = 0.003$) in the longer-term.
**CONCLUSION:** Pediatric cardiomyopathy patients who require high levels of support receive a survival benefit from heart transplantation that is not shared by patients not requiring intravenous inotropic or mechanical support.
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Heart transplantation (HTx) has been primarily responsible for the improved survival of children with dilated and restrictive cardiomyopathy observed over the past 3 decades.[1–6] This survival benefit is limited by donor supply and the time-limited vitality of the cardiac allograft.[7,8] Thus, the timing of the use of HTx in relation to heart failure severity and the appropriate allocation of the limited number of donor hearts are important components of the HTx process to maximize the survival benefits in children with cardiomyopathies.

Recent studies have found adult HTx candidates who do not require intravenous or mechanical support, classified as United Network of Organ Sharing (UNOS) status 2, may actually have an increased risk of short-term death if they

| Abbreviations | |
| --- | --- |
| heart transplantation | HTx |
| left ventricle | LV |
| Pediatric Cardiomyopathy Registry | PCMR |
| Pediatric Heart Transplant Study | PHTS |
| United Network for Organ Sharing | UNOS |

undergo transplantation, suggesting they should not be listed for heart transplantation.[9–11] However status 2 pediatric HTx candidates have been reported to have a survival benefit from HTx.[12]

This study was performed to determine the rates of death and clinical deterioration in children with pediatric cardiomyopathy after listing for HTx and to identify the clinical characteristics of these children that are associated with death or deterioration while waiting for an allograft. We used a data set created by combining the Pediatric Cardiomyopathy Registry (PCMR) and the Pediatric Heart Transplant Study (PHTS) and studied children listed in both registries. We hypothesized that children with cardiomyopathy listed for HTx without a need for inotropic, ventilatory, or mechanical circulatory support would have low rates of death, similar to those observed in adults status- HTx candidates.

## Methods

### Patients

This analysis used a cohort from a PCMR-PHTS merged database of children from 16 institutions who met the following inclusion criteria (1) enrollment in the PCMR, having presented with cardiomyopathy between January 1, 1990, and December 31, 2005; and (2) enrollment in the PHTS with a date of listing for HTx between January 1, 1993, and December 31, 2005.

The PCMR consists of a prospective cohort of children (aged <18 years) diagnosed with cardiomyopathy after January 1, 1996, and a retrospective cohort of children who were diagnosed with primary cardiomyopathy between January 1, 1990, and December 31, 1995. Inclusion and exclusion criteria and echocardiographic phenotypes (dilated, hypertrophic, restrictive, or mixed) have been previously described.[3,13] Data were collected annually from presentation until the study end points of death or HTx were reached. The PHTS is an event-driven, multi-institutional database that collects annual mortality and morbidity data on all children (aged <18 year) before and after HTx from time of listing.[8,14] Merging the PCMR and PHTS database allows the longitudinal follow-up of children from the time they present with cardiomyopathy through their course after HT. All participating PCMR and PHTS centers obtained Institutional Review Board approval for participation in each study and for merging the databases. The authors had access to all the data.

Patients were divided into 3 levels of heart failure severity at the time of listing for HT: severity 0—children who were on neither inotropes, mechanical ventilatory, nor circulatory support; severity 1—children on intravenous inotropes but not on mechanical ventilatory or circulatory support; and severity 2—children on ventilatory and/or mechanical circulatory support, with or without intravenous inotropes. These levels of support roughly correspond to the following old and new[15] UNOS urgency statuses for adults as: 0, status 2; 1, status 1or 1B; and 2, status 1or 1A, except for infants listed at age <6 month, where only urgency status 1, 1B, or 1A are used.

Patients were analyzed for the following outcomes after listing: death while waiting for HTx, death after HTx, a combined death after listing outcome incorporating deaths before and after HTx, and alive without HTx. The event "alive, removed from transplant list" was not analyzed because UNOS policy allows for patients to be inactivated (status 7) and remain on the list not receiving allograft offers but retaining time accrued while at status 1 or 2. Varying institutional policies regarding length of time a patient remained status 7 vs total removal from the list precluded a meaningful analysis of this event. Patients listed with severity score 0 were also analyzed for "deterioration," which was defined as HTx or death while waiting with a severity score that had worsened to 1 or 2. Demographic, echocardiographic, and clinical variables were ascertained for their association with outcome events.

### Statistical methods

Groups were compared with chi-square and Duncan's multiple comparison tests. Standard Kaplan-Meier analyses were used for actuarial survival analysis of death after listing for HTx (which includes death before and after HTx), death after HTxt, and analysis of deterioration in children listed with a severity score of 0. Parametric competing-outcomes methods were used to analyze multiple, mutually exclusive time-related outcomes (death, HTt, and alive free from HTx) after listing for HTx by severity score. This technique gives a more accurate representation of mortality while waiting for HTx, which can be overestimated if waiting list mortality is analyzed by Kaplan-Meier techniques that censor patients from the analysis at the time of other competing events (HTx).[16] Multivariate analysis in the hazard function domain was used to identify risk factors for deterioration among children with a heart failure severity score of 0 at listing. The analyses used SAS 8.2 software (SAS Institute, Cary, NC). A value of $p < 0.05$ was used to determine statistical significance.

## Results

### Clinical characteristics of the cohort

The study cohort consisted of 332 children (Table 1) who represented about 30% of the 1,129 children with cardiomyopathy listed for HTx in the PHTS during this period. The children were equally distributed among the heart failure severity classes: 115 had a score of 0, 118 had a score of 1, and 109 had a score of 2. Children on mechanical ventilatory or circulatory support (severity score of 2) at the time of listing were significantly more likely to be male, younger, and smaller than children in severity group 1 or 0. Children with a severity score of 0 (who were not receiving intravenous inotropic or mechanical support at listing) were, as a group, listed at a significantly longer time from their presentation with cardiomyopathy. Infants aged <6 months at listing, who have a different UNOS urgency status than that of older children, comprised 17% of the total cohort.

**Table 1**    Clinical Characteristics of 332 Children with Cardiomyopathy Listed for Heart Transplantation by Heart Failure Severity Scores at Time of Listing

| | Heart failure severity score[a] | | | |
| | 2 (n = 109) | 1 (n = 118) | 0 (n = 105) | |
| Characteristic | | | | p-value |
| --- | --- | --- | --- | --- |
| Boys, % | 60 | 47 | 44 | 0.03 |
| White, % | 69 | 62 | 73 | 0.19 |
| Age, mean years | 4.2 | 7.6 | 7.5 | <0.001 |
| Age <6 months at listing, No (%) | 34 (59) | 14 (24) | 10 (17) | <0.001 |
| Body surface area at listing (mean), m$^2$ | 0.7 | 1.0 | 0.9 | <0.001 |
| Time from presentation to listing, mean years | 0.2 | 0.6 | 1.3 | <0.001 |
| Cardiomyopathy phenotype, % | | | | |
| Dilated | 88 | 88 | 72 | 0.003 |
| Hypertrophic | 6 | 1 | 5 | 0.12 |
| Restrictive | 4 | 7 | 21 | <0.001 |
| LVFS, mean z-score | −9.4 | −9.2 | −6.5 | <0.001 |
| LV mass, mean z-score | 3.2 | 2.4 | 2.3 | 0.09 |
| Creatinine at listing, (mean) mg/dL | 0.74 | 0.60 | 0.54 | 0.004 |

LV, left ventricle; LVFS, left ventricular factional shortening.

[a]Score defined as 2 = children on mechanical ventilatory or circulatory support; 1 = children on intravenous inotropic support without mechanical support; 0 = children on neither intravenous inotropic or mechanical support.

The proportion of these infants with a severity score of 2 at listing (34 of 58, 59%) was significantly ($p < 0.001$) higher than that of infants with a score of 1 (14 of 58, 24%) or 0 (10 of 58, 17%).

Although a dilated cardiomyopathy phenotype was by far the most common in all the groups, children with a score of 0 had a significantly ($p < 0.001$) larger proportion of a restrictive phenotype. Left ventricular (LV) shortening fraction at presentation was markedly decreased in all groups but was significantly less depressed in children with severity scores of 0. Mean serum creatinine values at listing were significantly higher in children with a severity score of 2, despite an average younger age than the other groups, likely reflecting the greater severity of heart failure in this group.

## Outcome after listing for HTx

Deaths within 24 months after listing (before and after HTx) occurred in 21 of 109 patients initially listed with a severity score of 0 (5 before; 16 after); 39 of 118 patients listed with a severity score of 1 (10 before; 29 after), and 35 of 105 listed with a severity score of 2 (21 before; 14 after). Figure 1 shows the mortality at 12 months after listing (before or after HTx) was 26% in children with severity scores of 2, which was significantly ($p = 0.02$) higher than the 16% mortality among children with scores of 1 and the 9% among children with scores of 0. Mortality 12 months after HTx was 10% for children listed with severity scores of 2, 11% for children listed with severity scores of 1, and 7% for severity scores of 0. These mortality rates after HTx were not significantly different.

Virtually all of the events death before HTx, after HTx, or alive without HTx in children listed with a severity score of 2 (Figure 2A) or 1 (Figure 2B) occurred within 6 months

of listing. The 12-month mortality rate before HTx was the highest (20%) and the HTx rate was the lowest (69%) for children listed with a severity score of 2. Children with a score of 1 had substantially lower 12-month mortality before transplantation (8%) and a higher rate of transplantation (85%).

Patients with score of 0 had additional events 6 months after listing (Figure 2C). Only 3% of this group of children died before HTx 12 months after listing, and 82% received allografts. Very few events occurred more than 12 months after listing. At 24 months after listing, 4% of these children died before HTx, 87% received an allograft, and 9% were alive without HTx.
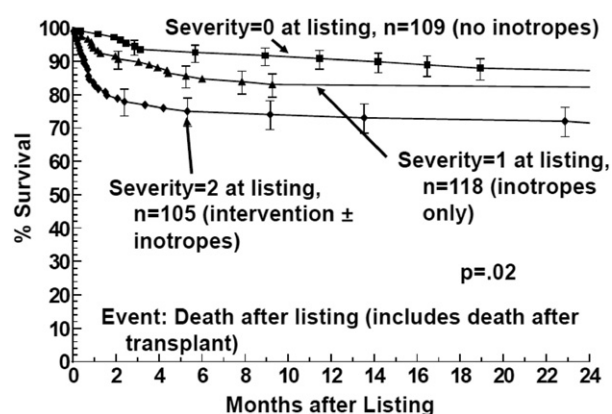


**Figure 1**    Survival after listing for heart transplantation among children with cardiomyopathy by heart failure severity score: 2 = children on mechanical ventilatory or circulatory support; 1 = children on intravenous inotropic support without mechanical support; 0 = children on neither intravenous inotropic or mechanical support.
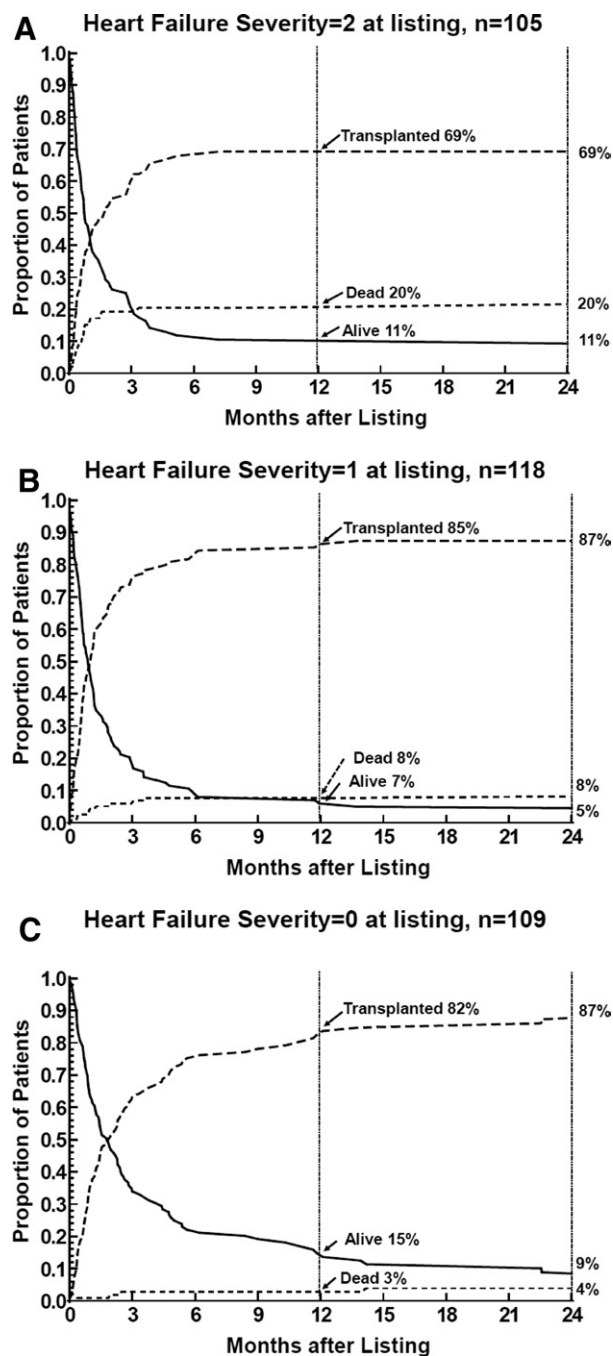
**A**    Heart Failure Severity=2 at listing, n=105

**B**    Heart Failure Severity=1 at listing, n=118

**C**    Heart Failure Severity=0 at listing, n=109

**Figure 2**    Competing-risk analysis of transplant, death without transplant, and alive without transplant in the first 12 months after listing among 332 children with cardiomyopathy by heart failure severity score: (A) children on mechanical ventilatory or circulatory support (severity score 2); (B) children on intravenous inotropic support, without mechanical support (severity score 1); (C): children on neither intravenous inotropic or mechanical support (severity score 0).

Thus, mortality after listing for children listed with severity scores of 2 primarily reflected mortality while waiting for an allograft. Mortality after listing for children listed with severity scores of 1 was relatively equally distributed between mortality before and after HTx. In children listed with a severity score of 0, mortality after listing primarily reflected mortality after HTx.

### Progression of heart failure severity in children listed for HTx with a severity score of 0

Although children with a severity score of 0 when listed for HTx had the best survival and the lowest rate of death before HTx, they frequently required increasing support while on the waiting list. Among the 95 children in this group receiving HTx, 31 (33%) had a severity score of 1 and 8 (8%) had a severity score of 2 at the time of HTx. Of the 5 children in this group who died before HTx, 1 had a severity score of 1, and 2 had scores of 2 at the time of death. Freedom from death or HTx with a severity score of 1 or 2 was 50% at 12 months after listing (Figure 3). The hazard function for deterioration was biphasic, with a high early peak in the first month after listing that declined over the next 5 months to a low, constant function.

Multivariate analysis (Table 2) identified 2 factors associated with an increased risk for deterioration of children with a severity score of 0 in the early and later, constant-hazard phases after listing. A history of surgery was significantly associated (relative risk, 3.84; $p = 0.03$, 95% confidence interval [CI], 1.13–13) with deterioration in the early phase. Cardiac surgical procedures were performed in 7 patients: 3 with restrictive cardiomyopathy (hilar node biopsy, tricuspid valve annuloplasty, resection of subpulmonary stenosis), 3 with dilated cardiomyopathy (pericardectomy, Batista procedure, suture of myocardial perforation), and 1 with LV noncompaction (pulmonary artery band). Lower LV shortening fraction $z$-score for age and sex at presentation demonstrated a nonsignificant trend towards an increased risk for deterioration 1 month after listing ($p = 0.07$), but lower LV mass $z$-score for age and sex at presentation demonstrated a significant late (constant phase) risk (relative risk, 1.74; 95% CI, 1.20–2.52; $p = 0.003$). Age at listing (including listing at age < 6 months), time from presentation to listing, year of listing, sex, ethnicity, body surface area, dilated cardiomyopathy phenotype, hypertrophic cardiomyopathy phenotype, restrictive cardio-
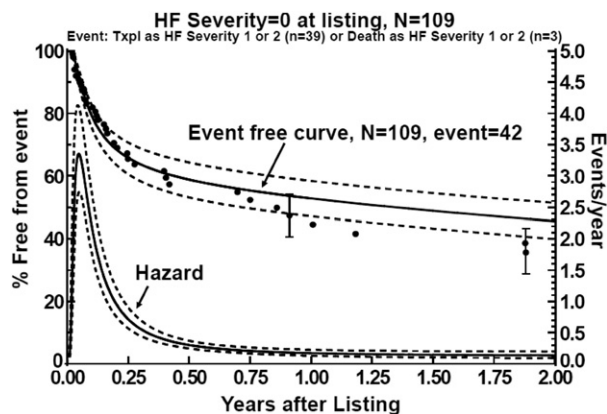


**Figure 3**    Freedom from deterioration in children with cardiomyopathy listed for transplantation not requiring mechanical or intravenous inotropic support (severity score 0). Deterioration was defined as death or transplantation with a severity score of 1 or 2. The bottom curve is the hazard function analysis of deterioration, demonstrating a high early phase hazard in the first 4 months after listing and a declining constant hazard.

**Table 2**  Statistically Significant Risk Factors for Deterioration among Children with a Heart Failure Severity Score of 0 at Listing for Transplant[a]

| Risk Factor | Early risk phase (≤1 month after listing) | | Constant risk phase (2–5 months after listing) | |
| --- | --- | --- | --- | --- |
| | RR (95% CI) | *p*-value | RR (95% CI) | *p*-value |
| History of surgery | 3.84 (1.13–13.0) | 0.03 | . . . | . . . |
| Lower fractional shortening z-score | 1.15[b] (0.99–1.34) | 0.07 | . . . | . . . |
| Lower LV mass z-score | . . . | . . . | 1.74[b] (1.20–2.52) | 0.003 |

CI, confidence interval; RR, relative risk.
[a]Deterioration was defined as transplantation or death before transplant with a worsening severity score of 1 or 2.
[b]Illustrates the increased risk with a 1-unit decrease in z-score.

myopathy phenotype, serum creatinine at listing, and M-mode echocardiographic measurements of LV end-systolic and diastolic dimensions or end-diastolic septal of posterior wall thickness were not associated with deterioration in univariate or multivariate analysis.

## Discussion

Our findings suggest HTx offers a survival advantage to critically ill pediatric cardiomyopathy patients requiring mechanical ventilatory or circulatory support, but not to children who do not require such support. These results are similar to those observed in adults showing the highest survival benefit from HTx occurs when the most severely ill patients receive an allograft.[9–11,17] Our findings, however, also mirror adult experience in that some status 2 adults can remain stable for long periods, but a significant proportion will decompensate and move to higher levels of urgency.[18]

Revisions in the UNOS adult heart allocation policy in 1998[15] and most recently in 2006[19] have occurred to direct donor hearts to the most critically ill patients with the goal of reducing mortality on the waiting list. Although some centers have not observed any benefits with these revised allocation algorithms,[20] the overall national impact has been an increased number of HTx and a reduction in wait-list mortality for adult HTx candidates requiring intravenous inotropic or mechanical support (adult UNOS status 1A and 1B). The decrease in the percentage of HTx occurring in status 2 patients was not accompanied by an increase in waiting list mortality.[21,22]

Our findings confirm results from a recent study[24] that found a much lower risk of death (<10%) before HTx in children with cardiomyopathy in status 1 (or now 1A) patients who required intravenous inotropic support than in those requiring mechanical ventilatory or circulatory support. This study also found that pediatric congenital heart patients listed for transplant as status 1 or 1A on intravenous inotropic support alone had a lower wait-list mortality (22.2%) than those listed on mechanical ventilatory support (31.1%) or extracorporeal membrane oxygenator support (33.2%).

A previous PHTS study[12] determined pediatric HTx candidates listed at urgency status 2 did receive a survival benefit from HTx. However, that study developed a model incorporating an overall high (19%) rate of death while waiting for HTx at status 1. That study included children listed for HTx with congenital heart disease, which is associated with a greater risk of death while waiting for an allograft than cardiomyopathies.[23,24]

Our study has a few limitations. Analysis of the deterioration observed in our group of children listed for HTx without intravenous inotropic or mechanical support is limited by the lack of data on the how long each patient who deteriorated received such support before death or HTx. However, among the 42 children initially listed with a heart failure severity score of 0 but who died or received an allograft with a severity score of 1 or 2, 3 (7%) died before HTx and 39 (92%) received an allograft. These proportions are similar to the proportions of 8% and 85%, respectively, of children listed for transplant with a heart severity score of 1 at 12 months after listing. Thus, an initial listing at a lower level of heart failure severity did not seem to impact the ultimate outcome for better or worse.

Our study is also limited by its inability to find many clinical characteristics that prospectively identify children who deteriorated on the HTx waiting list. An increased risk for deterioration in heart failure severity after a cardiac operation is not surprising. The observed relationship of lower LV mass to deterioration identifies a group of children, especially those with dilated cardiomyopathy, who might benefit from consideration of HTx at a low level of heart failure severity. Although our sample is relatively large, it may not be large enough to identify other variables that may have an effect on deterioration. Furthermore, other recently recognized[25,26] heart failure biomarkers that might help predict outcomes were not collected when the PCMR and PHTS were initiated in the early 1990s.

In conclusion, in children with cardiomyopathy, we found substantial differences in survival after listing for transplant, depending on the severity of heart failure at the time of listing. New therapies such as $\beta$-blockers in pediatric cardiomyopathy[27] have led to "delisting" for HTx in recent experience,[28] offering pediatric patients with less severe heart failure viable therapeutic options other than HTx. Certain extenuating circumstances, such as high reversible pulmonary vascular resistance, growth failure, or high risk of sudden death, may lead to justifiable and ben-

eficial use of HTx in children with cardiomyopathy who do not require high levels of support.[1,29] Improvement of survival benefit of HT by directing donors preferentially to the sickest children has been observed in the United Kingdom.[30] Our results support this type of strategy to achieve the optimal potential for HT to improve survival in children with cardiomyopathy.

## Disclosure statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

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