

# Increased Incidence of Hodgkin's Disease After Allogeneic Bone Marrow Transplantation

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**Purpose:** Immune dysregulation associated with allogeneic bone marrow transplantation (BMT) is linked to an increased risk of posttransplant lymphoproliferative disorders (PTLD); however, reports of Hodgkin's disease (HD) after transplantation are rare.

**Patients and Methods:** We evaluated the risk of HD among 18,531 persons receiving allogeneic BMT between 1964 and 1992 at 235 centers. The number of HD cases was compared with that expected in the general population. Risk factors were identified using Poisson regression and a nested case-control study.

**Results:** Risk of HD was increased in the postBMT population compared with the general population with an observed-to-expected incidence ratio (O/E) of 6.2 (observed cases,  $n = 8$ ; 95% confidence interval [CI], 2.7 to 12). A significantly increased risk of HD remained after excluding two human immunodeficiency virus-positive patients (observed cases,  $n = 6$ ; O/E = 4.7, 95% CI, 1.7 to 10.3). Mixed cellularity subtype predominated

(five of eight cases, 63%). Five of six assessable cases contained Epstein-Barr virus (EBV) genome. Posttransplant HD differed from PTLD by later onset ( $> 2.5$  years) and lack of association with established risk factors (such as T-cell depletion and HLA disparity). Patients with HD were more likely than matched controls to have had grade 2 to 4 acute graft-versus-host disease (GVHD), required therapy for chronic GVHD, or both ( $P = .002$ ), although analysis included small numbers of patients.

**Conclusion:** The increased incidence of HD among BMT recipients adds support to current theories which link overstimulation of cell-mediated immunity and exposure to EBV with various subtypes of HD. The long latency of HD after transplant and lack of association with risk factors for PTLD is noteworthy and should be explored further for possible insights into pathogenesis.

*J Clin Oncol 17:3122-3127. © 1999 by American Society of Clinical Oncology.*

**H**ODGKIN'S DISEASE (HD) is a malignant lymphoma typically accompanied by a spectrum of immune alterations.<sup>1</sup> Its unusual epidemiologic and biologic features suggest a relationship with a chronic infectious process. HD seems to be associated with at least two viral infections that alter the human immune system: Epstein-Barr virus (EBV) and human immunodeficiency virus (HIV)-1. Patients undergoing allogeneic bone marrow transplantation (BMT) experience severe immune dysfunction from intensive cytoreductive therapy, alloreactivity of the donor graft, and immunosuppressive drugs given as prophylaxis or therapy for graft-versus-host disease (GVHD). In this context, BMT

recipients have a high risk of posttransplant lymphoproliferative disorders (PTLDs), which usually develop in EBV-transformed donor B cells.<sup>2</sup> PTLDs occur mainly in the first 6 months after transplant and are associated with certain methods for in vitro T-lymphocyte (T-cell) depletion of donor marrow, use of polyclonal or monoclonal antibodies directed against T-lymphocytes in vivo, donor-recipient mismatch for HLA antigens, and use of unrelated bone marrow donors.<sup>3-6</sup> In contrast, few data suggest an elevated incidence of HD after BMT. This study, for the first time, evaluates the risk of HD in a well-defined population of more than 18,000 allogeneic BMT recipients. We examined potential risk factors and also performed molecular testing for the presence of the EBV genome.

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*Submitted November 5, 1998; accepted May 27, 1999.*

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*0732-183X/99/1710-3122*

## PATIENTS AND METHODS

The cohort included 18,531 patients who underwent an allogeneic BMT performed at the Fred Hutchinson Cancer Research Center, Seattle (FHCRC, 1969 to 1992;  $n = 4,149$ ) or at one of 234 transplant centers reporting to the International Bone Marrow Transplant Registry, Milwaukee (IBMTR, 1964 to 1990;  $n = 14,382$ ). Patients who received transplants as primary treatment for HD were excluded. Original pathology reports and diagnostic specimens of reported cases of lymphoproliferative disorders were obtained and reviewed (D.W.K., E.S.J.) to distinguish HD from non-Hodgkin's lymphoma or PTLD and confirm histologic subtype. Specimens were obtained for all eight reported cases of HD. In situ hybridization was performed to detect expression of EBV EBV1-encoded, as previously described.<sup>7</sup>

### Statistical Analysis

For each patient, person-years at risk were accrued from the date of transplant until the date of death, date of last follow-up, date of diagnosis of new primary cancer (including HD), or study end (December 31, 1992), whichever came first. Complete follow-up was available for 91% of patients. Age-, sex-, calendar year-, and region-specific incidence rates for HD were applied to the appropriate person-years to compute the expected number of HD cases. Significance tests of the ratio of the observed-to-expected (O/E) number of patients who subsequently developed HD and 95% confidence intervals (CIs) were calculated assuming a Poisson distribution. Excess risks were calculated as the observed number of HD cases minus the expected number per 10,000 person-years-at-risk. Poisson regression methods for grouped survival data were used to compare the risk of HD among subgroups of transplant recipients.<sup>8</sup> Because patients may differ in their cancer risk according to the disease for which the transplant was performed, data were stratified by primary disease in three categories (leukemia, severe aplastic anemia, and other). Patients were also stratified by time interval since BMT (< 2.5 years, 2.5 to 4 years, 5 to 9 years, and > 10 years) to account for the decline in the number of survivors over time after transplant. Univariate regression analyses were conducted, which were unadjusted for other confounding risk factors. Because of the small number of HD cases available for study (n = 8), the precision of the statistical modeling was necessarily limited. CIs and significance tests were calculated using likelihood ratio-based methods. All tests of significance were two-sided.

A nested case-control study was conducted to evaluate the effects of GVHD prophylaxis and treatment and adjusted for other potential risk factors. When possible, three controls per case were selected by random sampling from the BMT cohort. The controls were matched on primary disease, age ( $\pm$  3 years), sex, race, geographic region, degree of HLA compatibility, T-cell depletion (yes/no), and length of follow-up (at least as long as the interval between the transplant and HD diagnosis in the respective case patient). Detailed information on GVHD therapy (drugs and duration of therapy) were abstracted from transplant center medical records. Estimates of the relative risk (RR) of HD associated with GVHD therapy were calculated by comparing the treatment history of the case patients with those of their individually matched controls (within the matched-time interval) using conditional logistic regression methods.<sup>9</sup>

### RESULTS

Of the 18,531 transplant recipients included in the cohort, 75% underwent BMT for leukemia, 11% for severe aplastic anemia, and 14% for other diseases (Table 1). The median age at transplant was 26 years (range, < 1 to 72 years). Most patients (81%) received bone marrow from HLA-identical sibling donors. Transplant conditioning regimens included total body irradiation in 73% of patients, chemotherapy alone in 22%, and other regimens in 5%. Fourteen percent of patients received T-cell depleted bone marrow. Acute GVHD of grades 2 to 4 developed in 39% of patients, and extensive chronic GVHD developed in 30% of patients surviving at least 90 days.

Eight patients (four males and four females) developed HD at a median of 4.2 years (range, 2.9 to 9.1 years) after

**Table 1. Characteristics of Patients Who Underwent Allogeneic BMT**

Characteristic	No. of Patients	%
All patients	18,531	100.0
IBMTR	14,382	77.6
FHCRC	4,149	22.4
Sex, males	10,952	59.1
Primary disease*		
Acute lymphoblastic leukemia	4,139	22.3
Acute nonlymphocytic leukemia	5,063	27.3
Chronic myelogenous leukemia	4,770	25.7
Non-Hodgkin's lymphoma	682	3.7
Other malignancies	347	1.9
Severe aplastic anemia	2,114	11.4
Other	1,416	7.6
Donor-recipient relationship and histocompatibility		
HLA-identical sibling	15,072	81.3
HLA-mismatched sibling/relative	2,252	12.2
Unrelated donor	1,073	5.8
Other, uncertain	134	0.7
Transplant conditioning regimens		
TBI + Cy $\pm$ other drugs	11,985	64.7
TBI $\pm$ other drugs (no Cy)	1,532	8.3
LFI $\pm$ Cy $\pm$ other drugs	653	3.5
Busulfan + Cy $\pm$ other drugs	2,776	15.0
Cy $\pm$ other drugs	1,372	7.4
Other	213	1.1
T-cell depletion of marrow	2,561	13.8
Occurrence of acute GVHD, grades 2-4	7,231	39.0
Occurrence of extensive chronic GVHD†	3,972	30.0

Abbreviations: IBMTR, International Bone Marrow Transplant Registry; FHCRC, Fred Hutchinson Cancer Research Center; TBI, total-body irradiation; Cy, cyclophosphamide; LFI, limited-field irradiation.

\*"Other malignancies" include primarily multiple myeloma and solid cancers. "Other" primary diseases include myelodysplastic syndrome, myeloproliferative disease, lysosomal storage disease, hemoglobinopathies, thalassemia, sickle cell disease, and other smaller groups of primarily nonmalignant diseases.

†Occurrence and percent of chronic GVHD among 13,446 patients who survived  $\geq$  90 days.

transplant. Clinical features of these patients are summarized in Table 2. Four patients were transplanted for acute myelogenous leukemia, three for chronic myelogenous leukemia, and one for severe aplastic anemia. Most were adults at time of transplantation (median age, 21 years; range, 17 to 51 years). More aggressive types of HD predominated; five cases (63%) were mixed cellularity, two cases (25%) were nodular sclerosis, and one case (12%) was lymphocyte-depleted HD. In situ hybridization could be performed on tissue from six patients; five (83%) were positive for the EBV genome (using probes for EBV EBV1-encoded RNA), and one was EBV-negative. Of five patients who were tested for HIV-1, two were subsequently found to be serologically positive. HIV infection was unlikely in the three patients for whom HIV data were not

Table 2. Characteristics of Eight Patients Developing HD After Allogeneic BMT\*

Patient No.	Sex/Age at Transplant (years)	Disease	Conditioning Regimen	GVHD Therapy†	GVHD	Time From Transplant to HD (years)	HD Subtype	EBV (EBER1)	HIV Status	Survival After HD (years)
1	M/51	CML	TBI + Cy	CSA, Cy, STER	Acute 4, ext chronic	9.1	LD	Pos	Neg	2.5
2	M/18	AML	TBI + Cy	CSA, STER	Chronic suspected, not confirmed‡	2.9	MC	Pos	Pos	9.3§
3	F/21	CML	TBI + Cy, Daunorubicin	CSA, STER, AZA	Acute 1, ext chronic	7.2	NS	Pos	NA	7.8§
4	M/17	CML	TBI + Cy	MTX, AZA, STER, Cy	Acute 4, limited chronic	5.1	MC	Pos	Neg	6.0§
5	M/21	AML	TBI + Cy	MTX, STER, Cy	Acute 4	5.3	NS	NA	Neg	9.6§
6	F/19	SAA	Cy	CSA, Cy	Limited chronic	3.3	MC	Pos	NA	8.4§
7	F/31	AML	TBI + ARA-C	MTX, CSA, ATG	Acute 2	3.4	MC	Neg	Pos	3.8
8	F/23	AML	Bu + Cy	CSA, STER	Acute 2, limited chronic	3.2	MC	NA	NA	2.7§

Abbreviations: F, female; M, male; CML, chronic myelogenous leukemia; AML, acute myelogenous leukemia; SAA, severe aplastic anemia; TBI, total-body irradiation; Cy, cyclophosphamide; ARA-C, cytarabine; Bu, busulfan; CSA, cyclosporine; STER, steroids; AZA, azathioprine; MTX, methotrexate; ATG, antithymocyte globulin; ext chronic, extensive chronic GVHD; LD, lymphocyte depleted; MC, mixed cellularity; NS, nodular sclerosis; NA, not available.

\*All patients received marrow from HLA-identical sibling donors, without T-cell depletion.

†Therapy for GVHD given as prophylaxis or treatment.

‡No histologic confirmation of chronic GVHD, but patient was treated for suspected GVHD with CSA for 11 months.

§Alive at last follow-up.

||Patient had limited chronic GVHD with CSA therapy for 6 months.

available. Two of these latter patients (no. 3 and 6) were alive and without evidence of HIV-related disease after long posttransplant follow-up intervals (15 and 12 years, respectively). The third patient (no. 8) underwent transplantation after blood testing for HIV became commonly available and was observed for 6 years after transplant without evidence of HIV disease. Prognosis after HD diagnosis was generally favorable. One patient died 2.5 years after diagnosis of HD (11.6 years after BMT) from pneumococcal sepsis after splenectomy for recurrent HD. A second patient died 3.8 years after diagnosis of HD (7.2 years after BMT) from AIDS, with no evidence of recurrence of acute myelogenous leukemia (primary disease) or HD. The remaining six patients were alive at last follow-up (median, 8.1 years; range, 2.7 to 9.6 years) after diagnosis of HD.

The risk of developing HD in this cohort was significantly higher than would be expected in an age-, sex-, and calendar year-matched cohort in the general population, with eight observed (O) cases of HD versus 1.29 expected (E) cases (O/E ratio = 6.2, 95% CI, 2.7 to 12.2). The excess (absolute) risk of HD was 1.6 cases per 10,000 person-years at risk. No cases of HD occurred in the first 2.5 years after transplant (0.65 cases expected). However, HD risk rose to more than 12-fold higher than expected in the 2.5- to 4.9-year posttransplant interval (O = 4, O/E = 12.4; 95% CI, 3.3 to 31.8) and remained significantly elevated in the 5- to 9.9-year follow-up period (O = 4, O/E = 15.5; 95% CI, 4.2 to 39.7). HD

was not observed among patients who survived 10 or more years after the BMT (E = 0.06). A significantly increased risk of HD remained after excluding the two HIV-positive case patients (O/E = 4.7; 95% CI, 1.7 to 10.3). Most HD cases (n = 7) occurred in patients who underwent transplantation before 1985 (O/E = 11.5; 95% CI, 4.6 to 23.7). The risk seemed to return to normal after 1985, when only one case was observed (O/E = 1.5; 95% CI, 0.02 to 8.2).

Table 3 describes the results of univariate regression analyses, adjusted for primary disease and time since transplantation. No associations were observed with factors linked in previous studies to increased risks of PTLTD, eg, T-cell depletion of bone marrow (RR = 0.0), HLA mismatched or unrelated bone marrow (RR = 0.0), or the use of antithymocyte globulin (RR = 1.6). A marginally significant trend ( $P = .06$ ) for increasing risk with increasing severity of acute GVHD was observed, with a nearly five-fold risk seen for patients with grade 3 to 4 disease. No relationship was found with extensive chronic GVHD ( $P = .75$ ). Moreover, incidence of HD was not linked to age at transplant, sex, or radiation in the conditioning regimen. Similar results were found when these data were reanalyzed after excluding the two HIV-positive cases (trend of increasing severity of acute GVHD,  $P = .04$ ; acute grade 3 to 4, RR = 7.0,  $P = .04$ ; and extensive chronic GVHD, RR = 2.1,  $P = .37$ ).

**Table 3. Risk Factors for Posttransplant HD After Allogeneic BMT**

Model Variables	PYR	HD Cases	Relative Risk	95% CI	P
<b>Poisson Regression—Univariate Analyses*</b>					
T-cell depletion					
No	38,766	8	1.00	Reference	
Yes	4,528	0	0.00	—	.20
HLA					
Matched sib, 1 AG mis	41,265	8	1.00	Reference	
2 + AG mis, unrelated	2,029	0	0.00	—	.53
ATG prophylaxis or therapy					
No	40,257	7	1.00	Reference	
Yes	3,037	1	1.62	0.09-9.15	.67
Acute GVHD, trend					
None, grade 1	29,834	3	1.00	Reference	
Grade 2	7,550	2	2.32	0.30-14.00	Trend
Grade 3-4	5,910	3	4.77	0.88-25.81	.06
Chronic GVHD					
None/limited	31,415	5	1.00	Reference	
Extensive	11,879	3	1.27	0.26-5.17	.75
Model Variables‡	No. of Cases	No. of Controls	Relative Risk	95% CI	P
<b>GVHD Case-Control Study†</b>					
Minimal GVHD	0	12	1.00	Reference	—
Moderate/severe GVHD	8	11	∞	3.44-∞	.002

Abbreviations: PYR, person-years at risk, matched sib, matched sibling; 1 or 2 + AG mis, 1 or 2 + antigen-HLA mismatched related donor; unrelated, unrelated donor; ATG, antithymocyte globulin.

\*Eight HD cases, 18,531 patients, 43,294 PYR. Univariate Poisson regression models stratified by primary disease (leukemia, SAA, all other) and time since transplantation (< 2.5 yr, 2.5-4 yr, 5-9 yr, 10 + yr).

†Eight HD cases, 23 matched controls. Matched case-control analysis with controls matched to cases on primary disease, sex, age, geographic region, HLA compatibility, T-cell depletion, and matched time interval.

‡Minimal GVHD defined as acute GVHD grade 0-1 and no/minimal therapy for chronic GVHD; moderate/severe GVHD defined as acute GVHD grade 2-4 and/or chronic GVHD therapy ≥ 6 months.

A review of transplant center medical records determined that all eight patients who developed HD (100%), versus 11 (48%) of 23 matched controls, had either acute GVHD grades 2 to 4, or chronic GVHD requiring therapy for at least 6 months, or both (Table 3, RR = ∞; 95% CI, 3.4 to ∞; P = .002). Results changed only slightly after excluding the two HIV-positive cases (RR = ∞; 95% CI, 3.0 to ∞; P = .004). There was no evidence that overall duration of immunosuppressive therapy was related to risk (P = .71), although numbers of patients receiving long-term (≥ 2 years) GVHD therapy was small.

**DISCUSSION**

This report is the first to show a significantly increased risk of HD in a large, well-defined population of BMT patients. The risk was estimated at 6.2 times that expected based on general population rates (4.7 times the risk after excluding the two HIV-positive cases). EBV genome was detected in most assessable cases. Posttransplant HD was characterized by late onset (> 2.5 years after BMT),

generally good prognosis, and absence of previously-reported risk factors for PTLD. HD risk seemed to be associated with occurrence of acute GVHD and/or chronic GVHD requiring treatment, although analyses were limited by small numbers.

More than 25 years ago, Order and Hellman<sup>10</sup> compared HD to a civil war and suggested that the underlying pathogenesis of HD involved a reaction of normal T cells against virus-infected T cells similar to the reaction of donor T cells against host cells in GVHD. Considerable investigation has occurred since then, aided by tools of molecular biology. Recent evidence from single-cell analysis strongly suggests that HD has a B-cell origin.<sup>11,12</sup> Although the pathogenesis of HD is uncertain, some investigators postulate that the malignancy involves alteration of normal gene expression as a result of chronic antigenic stimulation of the cell-mediated arm of the immune system, possibly by EBV.<sup>1</sup> Evidence for EBV-positive tumors and GVHD was present in most of the HD cases in this study. GVHD after allogeneic BMT is associated with stimulation of donor cells by

recipient antigens and, as a consequence, impaired immune responses.<sup>13</sup> The spectrum of GVHD varies from mild and self-limiting disease to severe involvement of multiple organs with markedly high mortality.

In our cohort, the incidence of HD was substantially below that found for PTLD (78 PTLD cases, cumulative incidence of  $1.0\% \pm 0.3\%$  at 10 years).<sup>3</sup> We found that patterns of risk for HD contrast notably with those for PTLD. All eight HD patients in our series and three additional patients from the literature<sup>14</sup> who developed HD after BMT had long latency ( $> 2.0$  years after BMT) and a generally good prognosis, whereas most PTLDs develop within the first 6 months after BMT and are rapidly fatal.<sup>2</sup> Using simple univariate analyses (unadjusted for potential confounding variables), we observed no association with factors strongly related to PTLD risk, such as T-cell depletion of donor marrow, HLA mismatched/unrelated donor, and use of antithymocyte globulin. Larger numbers of HD cases with more robust regression models will be needed to fully contrast the risk profile for secondary HD versus PTLD. A high proportion of HD patients (five out of six) tested positive for EBV, which is also known to be involved in the pathogenesis of PTLD. If EBV contributes to the development of both HD and PTLDs, the difference in latency and risk factors suggests there may be substantial differences in mechanisms.

HD is reported in other immunosuppressed populations, such as persons infected with HIV-1,<sup>1,15,16</sup> recipients of solid organ transplants,<sup>17,18</sup> and those receiving immune suppression for mixed connective tissue diseases.<sup>19</sup> Among persons infected with HIV-1, the increased risk of HD is relatively modest compared with large excesses observed for non-Hodgkin's lymphoma (7.6-fold for HD *v* 113-fold for non-Hodgkin's lymphoma).<sup>15</sup> The six-fold increase in risk for HD seen among BMT patients is similar to that found among HIV-infected patients. Evidence for increased HD risk after organ transplantation is controversial, with one large study indicating excesses in females but not males.<sup>20</sup> Histologic and molecular characteristics of HD in solid

organ transplant recipients and HIV-1 infected subjects are similar to our patients, with mixed cellularity subtype predominant and most HD tumors testing positive for EBV RNA. In immunocompetent persons, EBV expression is found in approximately 30% to 50% of tumor tissue from HD cases,<sup>1</sup> and the mixed cellularity subtype comprises only a small proportion of HD in younger age groups in the United States.<sup>21</sup>

During the years in which our patients were treated for their primary disease and transplants were performed, HIV-1 contamination of then unscreened blood products was possible. Of the eight patients with HD, two were HIV-1-positive. In seropositive patients, the presence of HIV-1 may have been an additional factor contributing to the development of HD. Screening of blood products for HIV-1, in use since 1985, also may have eliminated an unidentified pathogen important for HD development accounting for the decreased risk in recent years. Alternatively, recent improvements in prevention and treatment of GVHD may also have contributed to this lessening of risk.

In conclusion, our study found that BMT recipients were at increased risk of developing HD several years after transplantation. Additional follow-up will be needed to determine if patients undergoing BMT in more recent years will also experience an increased incidence of this late complication. The unusual features of the HD cases observed in this series should stimulate further investigation into the epidemiology, clinical course, and molecular pathogenesis of HD in immunocompetent as well as immunosuppressed populations.

#### ACKNOWLEDGMENT

We are indebted to all collaborating investigators and staff from the participating transplant centers who contributed data to this study. We wish to thank Kathy Erne, Muriel Siadak, and Gary Schoch from FHCRC and Sharon Nell and Melodee Nugent from IBMTR for data collection and computing support. We acknowledge Kathy Chimes, Elena Adrianza, and Diane Fuchs from Westat, Inc. for coordination of field studies, and George Geise from Information Management Services for computing support.

#### APPENDIX

This study was supported by contract no. CP-51027 and CP-51028 from the National Cancer Institute. The Fred Hutchinson Cancer Research Center investigators were supported by grants no. P01-CA-18029, P01-CA-18221, and P01-CA-15704 from the National Cancer Institute and P01-HL-36444 from the National Heart, Lung, and Blood Institute. The International Bone Marrow Transplant Registry is supported by Public Health Service grant no. PO1-CA-40053 from the National Cancer Institute, the National Institute of Allergy and Infectious Diseases, and the National Heart, Lung and Blood Institute, of the United States Department of Health and Human Services, and grants from Alpha Therapeutic Corporation; Amgen, Inc; Anonymous; Baxter Healthcare Corporation; Bayer Corporation; Berlex Laboratories; Blue Cross and Blue Shield Association; Lynde and Harry Bradley Foundation; Bristol-Myers Squibb Company; Cell Pro, Inc; Centeon; Center for Advanced Studies in Leukemia; Chimeric Therapies; Chiron Therapeutics; Charles E. Culpeper Foundation; Eleanor Naylor Dana Charitable Trust; Eppley Foundation for Research; Genentech, Inc; Glaxo Wellcome Company; ICN Pharmaceuticals; Immunex Corporation; Kettering Family Foundation; Kirin Brewery Company; Robert J. Kleberg, Jr and Helen C. Kleberg Foundation; Herbert H. Kohl Charities, Inc; Nada and Herbert P. Mahler Charities; Milstein Family Foundation; Milwaukee Foundation/Elsa Schoeneich Research Fund; NeXstar Pharmaceuticals, Inc; Samuel Roberts Noble Foundation; Novartis Pharmaceuticals; Ortho

Biotech, Inc; John Oster Family Foundation; Jane and Lloyd Pettit Foundation; Alirio Pfliffer Bone Marrow Transplant Support Association; Pfizer, Inc; Pharmacia and Upjohn; Principal Mutual Life Insurance Company; RGK Foundation; Rockwell Automation Allen Bradley Company; Roche Laboratories; SangStat Medical Corporation; Schering-Plough Oncology; Searle; Stackner Family Foundation; Starr Foundation; Joan and Jack Stein Foundation; SyStemix; United Resource Networks; and Wyeth-Ayerst Laboratories.

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