

Feasibility and Efficacy of a Computer-Based Intervention Aimed at Preventing Reading Decoding Deficits Among Children Undergoing Active Treatment for Medulloblastoma: Results of a Randomized Trial

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Received April 30, 2013; revisions received November 20, 2013; accepted November 25, 2013

Objective To investigate the feasibility of a computer-based reading intervention completed by patients diagnosed with a brain tumor. **Methods** Patients were randomized to the intervention ($n = 43$) or standard of care group ($n = 38$). The intervention consisted of 30 sessions using Fast ForWord[®] exercises in a game-like format. Change in reading decoding scores over time since diagnosis was examined. Gender, race, parent education, parent marital status, and age at diagnosis were examined as covariates. **Results** 17 patients (39.5%) were able to complete the target goal of 30 intervention sessions. Females had significantly greater training time than males ($p = .022$). Age at diagnosis was associated with average training time/session for females ($r = .485$, $p = .041$). No significant differences were found in reading scores between the randomized groups. **Conclusions** The study was well accepted by families and adherence by patients undergoing radiation therapy for medulloblastoma was moderate. Suggestions for improved methodology are discussed.

Key words academic functioning; cancer and oncology; children; cognitive assessment; intervention outcome; longitudinal research; neuropsychology.

Introduction

Children who survive medulloblastoma (MB) have been found to experience treatment-related deficits in essential neurocognitive functions, impaired overall intelligence, and a high rate of academic failure (Butler & Haser, 2006; Dennis, Hetherington, & Spiegler, 1998; Mabbott, Penkman, Witol, Strother, & Bouffet, 2008; Mulhern & Palmer, 2003; Mulhern et al., 2005; Nagel et al., 2006; Palmer, 2008; Palmer, Reddick, & Gajjar, 2007). A considerable number of studies have concluded that

interventions to remediate these deficits are needed. While intervention studies are difficult and expensive to conduct, establishing efficacious remediation is critical to improving the quality of patient survivorship.

Early intervention studies employed a wide variety of techniques ranging from a compensatory memory notebook (Kerns & Thomson, 1998) to pharmacotherapy (Thompson et al., 2001). Each of these studies aimed at ameliorating a specific deficit and met with varying level of success. Among the first to take a more comprehensive

approach to cognitive remediation among pediatric cancer survivors were Butler and Copeland (Butler & Copeland, 2002). The pilot study involved combining methods used by clinical psychology, special education, and brain injury rehabilitation to produce a 50-hr one-on-one intervention aimed at improving cognitive skills over an extended study period. Results indicated positive effect on measures of memory and sustained attention but these gains failed to generalize to improved academic function. The intervention was also costly and time-consuming.

With the aim to improve generalizability, two pilot studies tested in-home computer-based cognitive rehabilitation programs (Hardy, Willard, & Bonner, 2011; Kesler, Lacayo, & Jo, 2011). Following an 8-week program, 17 pediatric cancer survivors, who were an average of 3 years posttreatment, demonstrated improved processing speed and cognitive flexibility as well as increased visual and verbal declarative memory (Kesler et al., 2011). Following a 12-week program, nine patients who were an average of 5.7 years off therapy showed increases in working memory index while their parents reported a decline in attention problems (Hardy et al., 2011). Together these studies lend support for the feasibility of computer-based interventions for use by survivors of pediatric cancer. However, no study to date has attempted a prophylactic approach, that is, to offer an intervention with the aim to eliminate or significantly reduce the deficit before it occurs.

In 2005, the academic achievement of 111 children who had been treated for MB was reported (Mulhern et al., 2005). These patients completed >200 assessments of academic skills over a 6-year study period, providing longitudinal standardized scores of reading decoding, spelling, and math. Of the three domains, it was clear that reading decoding ability showed great vulnerability, with patients both younger and older than 7 years of age demonstrating significant declines in reading decoding over time from diagnosis. Deficits in the ability to read have a far-reaching impact on the patient's future academic achievement, social acceptance, opportunity for vocational choice, and economic independence.

In response to the 2005 study (Mulhern et al., 2005), we conducted a randomized reading intervention study for children who were newly diagnosed with MB. The first objective of the study was to determine the feasibility of a randomized reading intervention completed by patients with MB during active radiation treatment. Children undergoing radiation treatment are required to attend appointments on a daily basis and are thus also available on a regular schedule for intervention training. However, it was unknown whether or not the families

would consent to the study and if patients could comply with the reading intervention while simultaneously undergoing active radiation therapy (RT). It was hypothesized that patients who were older at diagnosis would be more likely to complete the intervention training. The second objective was to compare the reading decoding and related skills of those who were randomized to the intervention arm to those who were randomized to the standard of care arm. It was hypothesized that those who were randomized to the intervention arm of the study would show significantly higher reading decoding ability over time.

Methods

Patients

Study participants were recruited from an institutional review board (IRB)-approved clinical trial for patients newly diagnosed with pediatric MB. Patients were considered eligible for the IRB-approved intervention study if they were being treated at the primary site, were of school age (at least 4 years old but not >21 years), English speaking, and able to complete a valid screening of reading decoding ability. Patients and their parent or guardian(s) were approached to discuss the patient's possible participation in the reading intervention study. On agreement, parents and/or patients signed a separate consent form distinct from the main medical treatment consent, and the patient was then randomly assigned to either the standard-of-care control group (SOC) or to the reading intervention (RI) group. Randomization was stratified according to risk-status (average vs. high) and age of the patient (<7 and ≥ 7). The patient was formally referred to the school program to begin intervention training and/or to receive standard of care services.

Patients were treated with postsurgical risk-adapted craniospinal irradiation (CSI) followed by four cycles of high-dose chemotherapy (cyclophosphamide, cisplatin, vincristine) with stem cell support. Average-risk patients received 23.4 Gy CSI, 3D conformal boost to the primary site to 55.8 Gy. High-risk patients received 36–39.6 Gy CSI and 3D conformal boost to the primary site to 55.8–59.4 Gy.

Randomization

Of the 126 MB patients enrolled, 41 were not eligible owing to posterior fossa syndrome ($n = 17$), poor medical status restricting valid assessment ($n = 2$), being outside the age criteria and/or not attending school ($n = 16$), and no English language ($n = 6$). This left 85 patients considered eligible for the study. Of the 85 eligible patients, 81 (95.29%) were randomized to either SOC ($n = 38$) or

Table I. Characteristics of Patients With Medulloblastoma ($n = 126$) and Their Parents ($n = 109$) by Group

Variable	Intervention	Standard of care	Not randomized
N	43	38	45
Gender			
Female	19	12	15
Male	24	26	30
Risk			
Average	30	27	27
High	13	11	18
Race			
Asian	3	0	1
Black	2	9	4
Other	2	3	5
White	36	26	35
Age at diagnosis			
Mean	9.38	9.27	9.84
Standard deviation	3.12	3.18	5.76
Parent age			
Mean	40.07	37.44	36.70
SD	7.06	7.07	7.32
Parent education			
Mean	15.12	14.02	13.64
SD	2.46	2.30	2.44
Parent marital status			
Married	33	22	25
Separated	3	5	2
Divorced	4	6	2
Single	0	5	2

to RI ($n = 43$). The parents of only four patients (4.71%) did not consent to the intervention study (see Appendix A). Demographic information by group is provided in Table I. Patients participated in RI and/or the SOC activities during the radiation phase of their treatment. During this phase, patients were scheduled to be at the hospital 5 days per week, for a period of at least 6 weeks. Appointments to attend the school program were added to the patient's daily schedule.

The patient was removed from the intervention study if the patient experienced an adverse event that resulted in his or her removal from the entire medical treatment protocol, or the patient withdrew. Patients were free to refuse continued participation at any time.

Standard-of-Care Control Group

Patients randomly assigned to the control group received the current standard of care with regard to educational services from the hospital School Program. Patients who are of school age attend up to three 1-hr sessions per week

with a licensed teacher, in either the K-6th or the 7-12th grade classroom. The goal of these sessions is to allow the patient to complete school assignments by using books and activities provided by the patient's community school. Similar services are also available for those patients who have graduated from the 12th grade and have college-level assignments. The arrival of curriculum books and assignments from the community school may sometimes be delayed but School Program staff has the option to use other curriculum materials to aid continuity of school services. If patients were not able to attend because of treatment-related challenges, school staff attempted to reschedule and gave them assignments to do on their own within housing as tolerated. Some school subjects like algebra or other math did not lend itself well to completing without the teacher, so school staff tried to concentrate on what help the child needed from the teacher when in the class, while allowing them to work on other subjects when away from the teacher. The patients in the RI group received the same modifications for their school sessions as did the SOC group.

Reading Intervention Group

Rather than develop an intervention, we chose to use a method validated for use with children, and that could be generalized to use outside the hospital or clinical environment, and that could be delivered in a time frame corresponding to the radiation phase of the patients' medical treatment. Previous studies served as the foundation for the reading training program commercially available as Fast ForWord[®], from the Scientific Learning Corporation (Merzenich et al., 1996; Tallal et al., 1996; Tallal, Merzenich, Miller, & Jenkins, 1998; Wright et al., 1997). Scientific Learning Corporation provided the training program at no charge. Fast ForWord[®] is a computer-based training system developed in response to scientific research on the development of reading ability and reading deficits. By using a game-like format that incorporates modified speech, the program seeks to improve reading skills through an intensive training schedule and adaptive programming. The Fast ForWord[®] program is widely used within schools and clinic settings.

In addition to receiving the standard-of-care educational services, patients randomly assigned to the RI group completed the Fast ForWord[®] computer-based training program with a goal of 48 min per day, 5 days per week, for 6 weeks. This resulted in a target training criteria of 30 sessions and total training time of 1,440 min. Once the patient completed the demonstration exercises and the teacher was satisfied that the patient understood the exercises and could use the computer effectively, the

intervention began. The participant's performance was monitored and number of minutes training was recorded by the program. No restrictions were made if the patient desired to continue beyond the target criteria.

Reading Assessment

Assessment of reading decoding was completed using the Woodcock Johnson, Third Edition (WJIII) Tests of Achievement (Woodcock, McGraw, & Mather, 2001), with particular attention given to the reading and reading-related abilities. Two subtests were completed: (1) Letter-Word Identification, and (2) Word Attack, a test requiring the patient to read phonologically regular nonwords. The combination of these two subtests provided a standardized composite score of overall reading decoding ability with a population mean of 100 and a standard deviation of 15. Scores of 90–110 are considered to be in the average range, while those 80–89 are considered low-average.

Measures of reading decoding were obtained at baseline (before beginning the RI), following the intervention phase of the study (postradiation), and yearly thereafter for a period of 5 years postdiagnosis. This approach allowed the evaluation of longitudinal efficacy of possible intervention-related improvements. SOC control patients received the measures at corresponding time points for the purpose of comparison.

The reading evaluations were completed within the psychology clinic within the hospital by licensed psychological examiners, while the intervention and control group services were received within the school program classrooms with licensed teachers. Each office held separate records resulting in the examiners being blind to each patient's randomized group assignment.

Statistical Analysis

On the basis of the analyses of historical data, we conducted a randomized study to compare the RI training program with the current standard of care to determine whether the RI training program can reduce the decline in the reading decoding composite score per year by 75%. Statistical analysis was completed according to the intent to treat principle. Therefore, all randomized patients were included in the analysis regardless of the extent of their intervention training. Adherence was examined using total intervention training time (minutes), number of sessions completed, and average training time per session. These variables were also examined for their association with patient age at diagnosis (years), gender, race, risk status (average vs. high risk), parent age at the time of

their child's diagnosis (years), parent education (years), and parent marital status (married or other).

Random coefficient models (RCM), a type of longitudinal data model, were used to estimate changes in reading decoding over time (Diggle, Liang, & Zeger, 1994; Laird & Ware, 1982). These models treat data from different patients as statistically independent while treating those from the same patient as correlated. RCM can also handle variations in the number of measurements per patient and allows estimation of the population or average rate of change (slope) over time, individual or patient-level rate of change, as well as differences in slopes between groups (Chambers & Hastie, 1993; Jones, 1993; Little, Milliken, & Stroup, 1996; Rutter, 1994; Searle, 1987). Time since diagnosis (years) was included as a continuous covariate in all analyses of the reading decoding test data. Randomization arm (RI vs. SOC), disease risk status (high vs. average risk), age at diagnosis (<7 vs. ≥7 years), and gender were considered as dichotomized variables. To be included in the RCM analysis, patients had to complete baseline evaluation plus at least one other assessment. The RCMs were fitted using PROC MIXED in SAS Release 9.2 (SAS Institute, Cary, NC). All *p*-values noted below are two-tailed, and an alpha level of *p* = .05 was used as a threshold for significance. No adjustments were made for the number of analyses performed.

Results

Intervention Adherence

Of the 43 patients with MB randomized to the RI group, one patient was too ill to begin the training, and two patients withdrew from the study after three RI sessions. However, owing to the intent to treat principle, these patients were included in the following analyses.

Overall, the group completed a median of 27 sessions (mean = 26.79) and had a median total training time of 1,207 min (mean = 1,206.30). However, there was large variability in the number of training sessions completed (range = 0–46 sessions, *SD* = 10.71) as well as in the total training time (range = 0–2,115 min, *SD* = 562.69). Seventeen of the 43 patients randomized to the RI (39.5%) were able to complete the target of 30 intervention sessions, and meet the goal of 1,440 total minutes of training. An additional 20 patients were able to complete at least half of the 30 sessions (46.5%, 15–29 sessions).

For the group as a whole, there was some suggestion in the data that age of the patient at diagnosis may be associated with average training time per session ($r = .263$, $p = .09$). Further examination of this relationship found age at diagnosis to be associated with minutes

Table II. Adherence to Reading Intervention Using Intent-to-Treat Principle of Analysis ($n = 43$) by Gender and by Risk Status of Patient

Variable	All patients $N = 43$	Gender		Risk status	
		Female $N = 19$	Male $N = 24$	Average $N = 30$	High $N = 13$
Sessions					
Mean (SD)	25.79 (44.87)	28.52 (9.35)	23.62 (11.4)	24.96 (9.15)	27.69 (13.9)
0–14	6 (14%)	1 (5.2%)	5 (20.8%)	4 (13.3%)	2 (15.4%)
15–29	20 (46.5%)	7 (36.8%)	13 (54.2%)	15 (50%)	5 (38.5%)
≥ 30	17 (39.5%)	11 (58%)	6 (25%)	11 (36.7%)	6 (46.1%)
Total training					
Time (min)	1,206.3 (562.7)	1,423.7 (474.8)	1,034.2 (575.9)	1,156.2 (520.6)	1,322.0 (657.7)
Mean (SD)					
0–1,220	21 (48.9%)	5 (26.3%)	16 (66.7%)	18 (60%)	3 (23.1%)
1,220–1,439	5 (11.6%)	2 (10.5%)	3 (12.5%)	2 (6.7%)	3 (23.1%)
$\geq 1,440$	17 (39.5%)	12 (63.2%)	5 (20.8%)	10 (33.3%)	7 (53.8%)

Note. Bold: significant difference between females and males, $p = .022$

trained per session for females ($r = .485$, $p = .041$), as well as for those treated as high risk ($r = .595$, $p = .041$), but not for male or average risk patients.

Females completed significantly greater total training time than male patients (mean = 1,423 and 1,034 min, respectively, $p = .022$), and on average significantly longer training time per session (female = 47.48 min/session, males = 42.80 min/session, $p = .024$). However, no significant differences were found between genders in the number of sessions completed (female = 28.5 sessions, males = 23.6 sessions, $p = .13$). No significant differences were found between average and high-risk patients on number of sessions, total training time, or average training time per session (Table II). Adherence was not significantly associated with years of parent education or parent age.

Change in Reading Ability Over Time

Patients were included in the statistical analysis of change in reading decoding ability over time if they had two or more reading assessments, including the baseline evaluation. Two patients randomized to the RI group, and four patients in the SOC group, were excluded due to having only a single assessment, which resulted in 385 observations for 75 patients (RI = 41, SOC = 34) over a 5-year follow-up period.

Observed baseline reading decoding scores were in the average range for both the RI group (mean = 104.1, $SD = 12.18$) and the SOC group (mean = 102.4, $SD = 15.18$) and were not significantly different from one another. Using a RCM of longitudinal data, including time and intervention arm (RI and SOC), the potential effect of the intervention over time with reading decoding scores as the outcome of interest was investigated. There was no significant difference in change over time

in reading decoding scores between the RI and SOC groups (RI = -1.51 points per year; SOC = -1.17 points per year; $p = .62$). In an expanded model, which included intervention arm, disease risk, age at diagnosis (< 7 years, ≥ 7 years), parent education, and the interactions with time, we observed higher baseline reading decoding scores for patients whose parents had higher levels of education (p -value = .0014). Further, patients with high-risk disease ($p = .0042$) and younger age at diagnosis ($p < .0001$) had steeper declines in reading decoding over time.

Post hoc analyses, using two separate RCM fitted to the RI group only, examined associations between change in reading decoding score and the following variables: (1) average minutes trained per day, age of the patient at diagnosis (< 7 years vs. ≥ 7 years), and disease risk status (average vs. high); and (2) total minutes trained over the course of the study, age of the patient at diagnosis (< 7 years vs. ≥ 7 years), and disease risk status (average vs. high). Patients who were older at diagnosis and who had average risk disease had less decline in reading decoding over time ($p = .0008$ and .0367, respectively). There was a trend toward average minutes trained per day being significantly associated with change in reading decoding over time, with those who trained longer per day having less decline over time ($p = .07$). However, the second RCM revealed no significant association for total minutes trained. Change in reading decoding over time (slope) was also examined by baseline reading score. No significant association was found.

In summary, there was no significant difference between RI and SOC group, and those with high-risk disease and younger age at diagnosis showed significantly greater vulnerability in reading decoding ability over time. Among

those who participated in the RI, total minutes trained was not significantly associated with outcome, while longer time trained *per day* trended toward significance.

Discussion

To our knowledge, the current study represents the first attempt at offering an intervention to pediatric patients during active treatment for MB. Approximately two thirds of patients newly diagnosed with MB were considered for participation. Of those not considered eligible, the majority suffered from surgery-related complications or other disease-related illness that restricted participation. As shown by the 95% consent rate among those eligible, families were receptive to the study. However, because the RI was conducted at the same time as patients were undergoing the radiation phase of medical treatment, difficulties in completing the required intervention “dosage” were experienced.

On average, the group showed moderate completion with regard to number of sessions and total training time on the intervention, with median rates nearing the target goals. However, there was large variation in completion rates among patients, with only 39.5% able to meet or exceed the target goal of 30 sessions and 1,440 training minutes. Three main barriers to completing RI sessions were observed and may be important determinants for future studies to consider: (1) daily sedation, (2) fatigue, and (3) nausea and vomiting. (1) Many patients had to be sedated for their daily radiation therapy. Therefore, we were not able to control scheduling of the RI sessions. The sedation, and variability in recovery from the sedation, had a marked effect on our patient’s stamina and demeanor toward completing the intervention sessions. Before sedation, patients tended to be hungry owing to necessary fasting, and after sedation, they were often groggy or moody. (2) While fatigue was not an issue at the beginning of the RI sessions, it became a salient factor toward the end of the radiation therapy phase, affecting the patient’s ability to get through all of their daily appointments. If the RI session was later in the day, it was often missed. (3) Most patients experienced some nausea/vomiting during the spinal phase of RT. Patients who were more severely affected prematurely ended their participation in the RI sessions.

In addition to the three common barriers to RI session completion, the patients’ schedule included regular physician visits, lab appointments, imaging procedures, and physical/occupational therapy. Medical appointments necessarily superseded the time set aside for the intervention. Some parents became overwhelmed with treatment side

effects or medical complications experienced by their child. Parents were presented with many difficult decisions, many of which they had to make with limited time, under emotional stress, and without the guidance they actively seek (Palmer et al., 2011). Much of the reality that treatment brings was unknown at the time of consent. While the families and care team began with the best of intentions toward the RI, survivorship of their child understandably moved to the forefront of their concerns, making it difficult to focus on possible long-term sequelae during active treatment. When their children asked not to participate any further, the parents agreed because, as parents specifically stated, the RI study was the only activity they felt they had the ability to end. All other aspects of treatment and care were essential to survival. These challenges are not viewed as unique to our study alone but rather they are salient issues that need to be closely monitored in any study attempting prophylactic intervention during active medical treatment. A more complete analysis of these issues could be carried out with intentional measurement of these important variables in future studies.

To increase enjoyment and motivation for the participants, several methods were used. The staff worked closely with each participant and did some “cheerleading” during the sessions, providing needed praise for active participation. Also, the area around each computer station included progress charts that provided direct weekly feedback to participants about their advancement in the RI sessions and provided weekly incentives for completion of sessions. While viewed as a positive influence, the medical issues mentioned above often overcame the gains made with the reinforcement methods. A more significant change in the program developed when we offered RI participants the opportunity to use a laptop to complete the sessions at a time that was most convenient for them and in a more relaxed setting such as the patient housing facilities. However, this option was only successful for those patients who were self-motivated or who had parents who could provide assistance. At the time of the study, laptops were not equipped with software for patients to complete school assignments. Therefore, laptops were not available to patients for completing school assignments.

Offering an intervention during the radiation phase of the patient’s treatment provided accessibility to the patient but also presented many challenges that could not be overcome owing to the inherent nature of the treatment itself. An improved study approach may be to use the accessibility to establish the patient’s familiarity with a computer-based intervention, and train the parent(s) or guardian(s) how to use the data upload features of the program. The patient could then complete an intervention during

the rest period that occurs between the radiation and chemotherapy phases of treatment. This may reduce disruptions and increase completion rates, while still allowing the patient's progress to be monitored by school program staff.

Despite the difficulties faced with implementing an intervention during active treatment, we feel strongly that it was a valuable effort. The more common, and often frustrating, "wait to fail" approach is not acceptable. Many school districts have policies that restrict access to support services until students have fallen below specific cutoff scores. This study attempted to intervene before failure or significant decline occurred, thereby taking a preventative approach.

Previous literature has shown that lower socioeconomic status, minority group status, and high family stress are associated with attrition from child and family mental health services (Kazdin, Holland, & Crowley, 1997). The current study did not find a significant relationship between completion rates and years of parent education or parent marital status. In addition, no significant differences were found by race. However, older female patients and older high-risk patients were found to have higher average training times per session. This partially supports our hypothesis that older patients would be more likely to complete the training.

Female patients were found to train for significantly longer period per session and had greater total training time, than male participants. Studies of gender differences in academic achievement, grade attainment, and study habits show that girls have an advantage over boys, and that these differences are influenced by personality and behavioral factors (Aluja & Blanch, 2004; Duckworth & Seligman, 2006; Pomerantz, 2002; Wentzel, 1988). Pomerantz, Altermatt, and Saxon (2002) found that girls in the study experienced better academic performance, but more internal distress than boys. This distress was hypothesized to be related to a greater concern for pleasing adults, causing an increase in girl's motivation to do well in school. Aluja and Blanch (2004) found that girls in the study exhibited more self-discipline and were good in conforming in the classroom. Additionally, they concluded that these personality factors were related to better study habits and academic achievement. Duckworth & Seligman (2006) found that girls in their study were better than boys in self-discipline and had greater GPAs at the end of the school year than their male peers. Given that the RI sessions were done in a school setting and supervised by School Program personnel, it may be that similar factors influenced girls in being more compliant with the sessions.

Unlike a recent intervention study with survivors of pediatric cancer (Hardy et al., 2011), we did not observe

a significant relationship between the intervention and the outcome of interest over time. The protocol-driven intent-to-treat principle used for analysis, and the related large variance in completion rates, may have reduced the power to statistically detect differences between the RI and SOC arms. Those with higher average training times per session showed a trend toward a more positive change in reading decoding over time, but this association failed to reach statistical significance. Similarly, total training time over the course of the study was not significantly associated with outcome.

It may be that the SOC services also provided benefit, thus reducing the ability to statistically perceive the impact of the RI. In addition, parents were free to obtain services for their child outside of the clinic setting. Documenting and accounting for any such services and including the data in the analyses would improve the study methodology. Regardless of randomization, or potential outside services, patients who were treated as high risk and who were younger at diagnosis, continued to show greater vulnerability to declines in reading decoding ability. Perhaps these patients experienced reading difficulties due to negative impact on visual processing that would warrant a different approach to reading remediation. Further study is encouraged.

The current study was an ambitious attempt at testing a prophylactic intervention offered during active treatment, aimed at ameliorating reading deficits found to be prevalent in previous study (Mulhern et al., 2005). The study was well accepted by families and patients were able to moderately comply with the intervention while undergoing radiation therapy for MB. Continued testing of varied approaches is critical to discovering methods to improve neurocognitive late effects for survivors of childhood brain tumors.

Funding

National Cancer Institute through a Cancer Center Support (CORE) (P30-CA21765), the Noyes Brain Tumor Foundation, Musicians Against Childhood Cancer (MACC), and American Lebanese Syrian Associated Charities (ALSAC).

Conflicts of interest: None declared.

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