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Monitoring and Assessment of Neuropsychological Outcomes as a Standard of Care in Pediatric Oncology

Robert D. Annett, PhD,[1]* Sunita K. Patel, PhD,[2] and Sean Phipps, PhD[3]

Central nervous system cancers or exposure to CNS-directed therapies increase risk for neuropsychological deficits. There are no accepted guidelines for assessment of neuropsychological functioning in this population. A multifaceted literature search was conducted and relevant literature reviewed to inform the guidelines. Studies of neuropsychological outcomes are widely documented in the pediatric oncology literature. There is strong evidence of need for neuropsychological assessment, but insufficient evidence to guide the timing of assessment, nor to recommend specific interventions. Children with brain tumors and others at high risk for neuropsychological deficits should be monitored and assessed for neuropsychological deficits. Pediatr Blood Cancer 2015;62:S460–S513.

Key words: children; neuropsychology; outcomes

BACKGROUND

Pediatric cancers affecting the central nervous system (CNS) are a broad collection of diseases including brain tumors and others where therapy can directly impact brain function. The American Academy of Pediatrics (AAP) identifies nzeuropsychological follow-up as a critical component to the care of children who have CNS cancers and are cancer survivors.[1] That report, based upon guidelines from the Children's oncology group, identifies that late effect risks are proportional to the intensity of therapy and that, in general, longer treatment with higher cumulative doses of radiation, higher doses of chemotherapy, and multimodal therapies increase the risk of late effects. Neuropsychological late effects of cancer and cancer therapy may not become manifest for a number of years, requiring ongoing health surveillance.[2]

In this article, we propose two broad groups of children where neuropsychological monitoring and assessment have sufficient evidence to warrant guidelines: a) children diagnosed with brain tumors who are currently in treatment or post treatment; and b) children with cancer who receive CNS-directed therapies that are in treatment or post treatment. This latter body of literature is primarily reflective of children with acute lymphoblastic leukemia (ALL). Throughout this article, the terms monitoring and assessment are used as distinct processes. Monitoring refers to a broad range of activities intended to screen for potential neuropsychological changes, and that might be conducted by a variety of disciplines, including physicians, nursing, psychology, and other allied health professionals. Activities might include interview of the patient or parent regarding school performance, use of standardized self- or parent-report measures, or administering of screening tools such as from the NIH toolbox, the CogState battery or abbreviated neuropsychological screenings.[3–6] Assessment is used to denote a more comprehensive procedure involving several performance-based measures that would typically require a licensed psychologist.

Children with brain tumors or other cancers receiving CNS-directed therapies have both immediate and long-term sequelae that impact brain development. The child's age at the time of diagnosis as well as the type and intensity of treatments (neurosurgical procedure, radiotherapy, chemotherapy) are likely to adversely impact both cortical and subcortical pathways of children's brain function.[7–9] Growing evidence indicates that core neuropsychological processes involved in brain function that can be adversely impacted include the following: general intelligence, attention, memory, language, executive functions (e.g., inhibitory control, working memory, cognitive flexibility), neurosensory functions, perceptual processing, and processing speed. These neuropsychological functions appear to directly impact functional outcomes such as academic achievement, adaptive functioning, and psychological adaptation.

Psychosocial Standard of Care

Children with brain tumors and others at high risk for neuropsychological deficits as a result of cancer treatment should be monitored for neuropsychological deficits during and after treatment.

As part of a project to create evidence-based standards for psychosocial care of children with cancer, we systematically examined the body of literature regarding pediatric neuropsychological assessment for children with cancer and CNS-directed therapies (e.g., ALL) to identify evidence in support of a standard of care. Our secondary aim is to link studies of neuropsychological assessment with studies that inform the timing of monitoring and assessment as well as highlight interventions have been developed, utilized, and evaluated with these populations (e.g., cognitive rehabilitation and pharmacotherapy).

METHODS

This review was performed as part of the collaborative *Standards for Psychosocial Care of Children with Cancer and Their Families* effort. For a full description of the methods used to

Abbreviations: AAP, American Academy of Pediatrics; ALL, acute lymphoblastic leukemia; CNS, central nervous system; TBI, total body irradiation

[1]Universityof Mississippi Medical Center, Jackson, Mississippi; [2]City of Hope Medical Center and Beckman Research Institute, Duarte, California; [3]St. Jude Children's Hospital, Memphis, Tennessee

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*Correspondence to: Robert D. Annett, Department of Pediatrics, Blair E. Batson Hospital for Children, University of Mississippi Medical Center, 2500 N State Street, Jackson, MS 39216-4505.
E-mail: rannett@umc.edu

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develop each standard, refer to Wiener et al.[10] A multifaceted search strategy was implemented that included PubMed and PsychInfo that was further refined through additional author-specific searches. The search strategy included the years 1995 until 2015. Search terms included the following: pediatric brain tumor, cancer, ALL, children, neuropsychology and cancer, neurocognition and childhood cancer, cognitive function and cancer, children and cancer, and (intelligence, attention, memory, language, executive functions, neurosensory, perceptual processing, processing speed, neuropsychological, bone marrow transplantation) cognitive remediation, cognitive intervention, rehabilitation, pharmacotherapy and cognitive and cancer. Search results were inspected for inclusion criteria, including the following: peer reviewed journal, child age birth-18 years (including some follow-up studies where children were diagnosed with cancer and then seen as young adults), and meta-analyses. Resulting studies were reviewed for inclusion criteria as well as bibliographic citations that could further inform the search. Exclusion criteria included non-English language publications, book chapters, and on-line publications that were not indexed in PubMed and PsychInfo.

RESULTS

Studies of neuropsychological outcomes using individual performance-based measures are widely documented in pediatric cancer research. A Summary of Evidence Table is available as Table I. Cross-sectional studies were commonly found in the search process. These studies indicate the presence of deficiencies and deficits in children's neuropsychological function arising from individual and combination treatments for brain tumors and CNS-directed therapies. We have identified 19 studies that have prospectively examined neuropsychological functioning in children with brain tumors and CNS-directed therapies.[11–30] Several general and systematic reviews (n = 24) and meta-analyses (n = 5) provide evidence examining child neuropsychological function following treatment for a brain tumor and other cancers with CNS-directed therapies (i.e., ALL).[31–36]

Neuropsychological Outcomes

Key domains of neuropsychological assessment that were supported by the pediatric cancer literature included the following: intelligence,[7,11,14,17,19,23,32,36–73] attention,[7,24,25,32,47,48,58,62,64,71,74–82] memory,[7,13,18,19,25,36,43,44,58,64,66,67,71,82–90] language,[36,40,66,86,91] executive functions (including inhibitory control, cognitive flexibility, working memory),[9,17,24,25,50,53,67,76,77,80,82,86–89,92–103] neurosensory functioning,[36,41,44,48,61,65,76,83,104] perceptual processing,[7,54,105] and processing speed.[17,24,58,75,76,78,79,84,87,98,106–108]

Studies examining neuropsychological outcomes in survivors of brain tumor have documented that longer times from diagnosis/treatment are associated with greater deficits in global IQ, academic functioning, and specific neuropsychological domains including attention, memory, executive functions, and processing speed.[36,67] There is established evidence for children with brain tumors that child age at diagnosis and treatment impacts observed outcomes, with younger age associated with increased risk for impairment.[8,109,110] Child age and intensity of treatment have also been predictive of neuropsychological outcomes for children with ALL.[111–113] Evidence for the impact of CNS-directed therapy for bone marrow transplantation offers relatively weak evidence for interval neuropsychological change,[15,16,26–30,114–120] although the evidence points to younger children (particularly those <3 years) who receive total body irradiation (TBI) as being the subgroup at highest risk.[30]

Longitudinal studies are more rare, but have also pointed to a decline over time in global IQ and most neuropsychological indices among patients with brain tumors. Linear modeling suggests declines of 1.5–2 points per year in first 5 years post radiotherapy treatment for brain tumors, without consistent evidence of nadir or leveling off.[25,71,110,121–124]

Timing

There is insufficient evidence to guide the specific timing of comprehensive neuropsychological assessment for children with brain tumors and ALL. However, given the available evidence of long-term sequelae, clinicians should be vigilant of possible neuropsychological changes, and engage in frequent monitoring for such changes. Monitoring should occur intermittently during the acute treatment phase, and regularly at follow-up visits following completion of treatment. Monitoring should ideally include a time-efficient yet sensitive screening of neuropsychological function

TABLE I. Summary of Evidence Table—Neuropsychological Assessment

Standard	Evidence summary[1]	Methodology[2]	Quality of evidence[3]	Strength of recommendation[4]
Children with brain tumors and others at high risk for neuropsychological deficits as a result of cancer treatment should be monitored for neuropsychological deficits during and after treatment	Empirical research for brain tumors indicates significant impairments associated with tumor and treatment	Cross-sectional; longitudinal studies; significant replication of findings	High	Strong recommendation, given the impact of disease and treatment factors on later neuropsychological functioning
	Evidence gaps: prospective research still needed to assess long-term neuropsychological deficits with other malignancies	Large scale follow-up studies; clinical trials group consensus	Quality of evidence given consistent findings from numerous well-designed studies	

[1]Based on summary of evidence table for that standard; [2]Types of studies: e.g., RCT, cross-sectional, longitudinal; consensus; systematic review articles; [3]Quality of evidence: high = A, moderate = B, low and very low = C (based on GRADE criteria); [4]Strength of recommendation: strong = 1, weak = 2 (based on GRADE quality criteria).

with standardized measures. Questioning of the patient and/or parent regarding any perceived changes, such as declining school performance, memory loss, or difficulty with attention and concentration is critical, especially if screening of neuropsychological function is not feasible. Referral for a comprehensive neuropsychological assessment should be considered when there is evidence of any such changes. The rate of decline documented in the literature for children with brain tumors appears sufficient to indicate that a comprehensive neuropsychological assessment 2–3 years from the time of diagnosis would identify functional deficits, though this timing is not optimal for reintegration planning for school aged children. Thus, consideration should be given to obtaining an assessment upon completion of treatment, in order to facilitate school entry/re-entry, and to obtain a baseline assessment that provides a context for appreciation of any subsequent changes. Completion of treatment will vary by disease and the specific treatment protocol. This will require the attention of the care team to identify when this point occurs for a child so that a referral can be made in a timely manner. Follow-up assessment would then be recommended at 2–3-year intervals, or in the events of suspected cognitive changes, and statistically meaningful changes in a child's neuropsychological profile.

Interventions

A large multisite study of 161 total survivors, along with several studies employing a small number of survivors of brain tumor and/or ALL *randomized* to a cognitive remediation arm showed positive benefits on parent-report measures and selected objective tests compared to a control condition.[125] However, the trial did not demonstrate improvement in the intended outcome of attention functioning. Cognitive intervention programs have thus far included computerized "game-like" activities, various cognitive behavioral and learning strategies, and prescriptive activities focused on a single academic area such as mathematics.[125–136] A pilot parent training directed at promoting effective learning strategies within the home has shown improved child academic performance, the study's primary outcome, and therefore has promise for educational outcomes.[137]

Pharmacotherapy approaches to improve attention dysfunction have included psychostimulant medications (e.g., methylphenidate) and acetylcholinesterase inhibitors (e.g., donepezil).[35,138] Studies involving survivors of brain tumor and ALL demonstrate significant improvement on parent report ratings. Higher baseline IQ, males, and older age at treatment predicted better response to 0.60 mg/kg dose of methylphenidate in the cohort.[20,106,138–143]

Barriers to Care

There are significant clinical care barriers to implementation of the proposed guideline, notably the availability of pediatric neuropsychology specialists, the costs of comprehensive neuropsychological assessment, and inconsistent reimbursement for such services by third party payors. In addition, there is a need to increase capacity within pediatric caner teams through training in screening procedures for neuropsychological functioning that could be employed. Table II provides a brief overview of barriers that have been identified and potential solutions.

DISCUSSION

Assessment of child neuropsychological functioning is supported by empirical findings demonstrating impairments for survivors. Both acute and long-term neuropsychological sequelae are consistently observed among children with brain tumors. In contrast, evidence suggests that neuropsychological impairments for children with ALL are less evident during the period of active treatment, yet long-term sequelae do emerge, albeit at a less severe level compared to children who have brain tumors. Thus to attempt to capture dynamic brain function changes that occur, the currently available evidence supports regular monitoring of neuropsychological functioning integrated with routine clinical care during and particularly after treatment. Monitoring can serve as a valuable tool for early identification and subsequent referral for more comprehensive assessment procedures. In addition to monitoring neuropsychological functioning, we suggest that developmental delays and learning difficulties be included in the monitoring procedures. Where our evidence lags is in determining the specific timing for neuropsychological assessment, and identifying which types of interventions should be implemented. Moreover, a substantial gap exists regarding evidence-based monitoring strategies with known sensitivity/

TABLE II. Barriers and Response to Barriers for Neuropsychological Assessment of Children With Brain Tumors and CNS-Directed Therapies

Barrier	Response to barrier
Multidisciplinary screening with expertise in assessment of neuropsychological functioning and pediatric cancer late effects	1. Training of pediatric cancer team in screening procedures that can identify children with risk factors or acute mental status changes
Pediatric neuropsychologist not available at the center	1. Programs can prioritize this service as an essential part of acute and late effects care 2. Programs can create a systematic way that neuropsychological monitoring and assessment will be provided in the clinical setting 3. Partnerships can be developed with existing pediatric neuropsychological providers from other clinical services (e.g., pediatric neurology)
Reimbursement for neuropsychological monitoring and assessment services vary by state, with some states requiring a mental health diagnosis for reimbursement	1. Children's hospitals need to ensure support for improving billing mechanism and efficiency for reimbursement for clinical services 2. Work with national professional and consumer groups to lobby for mandated coverage for these indicated services

specificity. Yet there is reason to consider that monitoring of neuropsychological functioning could best be completed by a psychologist with expertise in cancer effects and late effects of treatment. The timing for monitoring is debatable, with little evidence to guide this element of care. Nonetheless, we suggest that monitoring begins several months after diagnosis, and using clinical judgment, as necessary during treatment to the time when a comprehensive neuropsychological evaluation is indicated.

A research gap in need of improvement is the development of standardized methods and measures for screening/monitoring neuropsychological functioning in children with cancer. While processes and measures exist for developmental surveillance in pediatrics,[144] no disease-specific childhood cancer tools exist at present. However, measures with validated sensitivity and specificity employed in general pediatrics may be useful for children up to early school age, though are not without some controversy.[145–147] For the larger population of children and adolescents, there are no similar measurement systems for neuropsychological function, though screening and monitoring may be completed with broad based behavioral measures.[96,148–150]

The interventions reviewed typically were provided within the context of a research study, thus ensuring fidelity with the intervention procedures, but with most lacking the practicality of real world interventions. Thus, they are not currently routinely available outside the context of research protocols.

Limitations within this review include no attempt to statistically examine the impact of child age and other influential features (e.g., socioeconomic status) upon groups of children that contributed to the studies presented. Moreover, studies are limited in the information that is provided regarding the content of the interventions that may have occurred for the participants.

In summary, the proposed standard, derived from the existing body of research, serves to provide improvements in care for children with cancer, as well as guide the future of pediatric research in this area. There are barriers to overcome; yet with providing a framework for assessment that is linked to intervention, we can provide an impetus to improve the life of children with cancers affecting the CNS.

CONCLUSION

Children with brain tumors and others at high risk for neuropsychological deficits as a result of CNS-directed cancer treatment should be monitored and assessed for neuropsychological deficits during and after treatment. Domains for neuropsychological monitoring include procedures for mental status changes as a result of treatments received. Domains of neuropsychological assessment via culturally appropriate assessments administered to the youth with cancer need to include the following: intelligence, attention, memory, language, executive function, neurosensory functioning, perceptual processing, and processing speed. Academic achievement should be included as a functional outcome.

The timeline for neuropsychological assessment for children with a pediatric brain tumor and child receiving CNS-directed therapy begins with the multidisciplinary screening at the time of diagnosis and at times of child acute mental status change. A comprehensive assessment should ideally occur after treatment has ended, followed by a re-assessment at 2–3 years after treatment or when monitoring is suggestive of significant neuropsychological or functional changes.

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SUPPLEMENTARY INFORMATION

SUPPLEMENTAL TABLE I: Neuropsychological Evidence Table

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Aarsen FK, Paquier PF, Arts WF, et al. Cognitive deficits and predictors 3 years after diagnosis of a pilocytic astrocytoma inchildhood.J Clin Oncol. 2009;27:3526-32.	4a	61 children (diagnosed between 3-11 years of age) with PA. Mean follow up period was 3 years 6 months (range 2-5 years)	To assess cognitive deficits and predictors 3 years after diagnosis of pilocytic astrocytoma (PA) in a consecutive series of pediatric patients treated for PA in different parts of the brain	• Problems with sustained attention and speed were present in all children with PA, regardless of tumor location. • Distinct cognitive profiles found in each defined tumor group: • Infratentorial (n = 29): deficits in language, vis-spat memory, exec fx • Supratentorial (n = 26): selective attention, exec fx. All had normal IQ* (This group did not have radiation therapy and had well-controlled epilepsy) • Severity of ventricle dilation at time of diagnosis and assessment was risk factor for development of deficits in attention, language comprehension and exec fx. Presence of a VP shunt was associated with better NP scores. This "suggests that treatment of hydrocephalus even if ventricle width is not progressing could prevent LT cognitive deficits after BT treatment" • Younger age at diagnosis, older age at assessment, and longer time window between dx and assessment were associated with more severe NP impairment • Chemotherapy was associated with better NP outcome than radiation
Anderson VA, Godber T, Smibert E, et al. Impairments of attention following treatment with cranial irradiation and chemotherapy in children. J Clin Exp Neuropsychol. 2004;26:684-97.	4b	Children 9-16 years; CRT+chemotherapy (n = 35); (ii) chemotherapy alone (n = 19); (iii) healthy children (n = 35)	Investigated attention and information processing skills, predicting that these skills would be impaired due to the vulnerability of cerebral white matter in early childhood	• Children treated with CRT+chemo, results identified residual deficits in processing speed for complex tasks, selective and shifting attention. Processing speed was intact for simple tasks, and there was no clear evidence of deterioration in performance over time, as might be expected in the presence of a sustained attention deficit. • Children treated with chemotherapy alone demonstrated generally intact attentional skills. This group did record an increasing number of attentional lapses over time on tasks tapping sustained attention skills.
Anderson FS, Kunin-Batson AS. Neurocognitive late effects of chemotherapy in children: the past 10 years of research on brain structure and function. Pediatr Blood Cancer. 2009;52:159-64.	7	NA	Review examines the state of the literature on neurocognitive late effects after chemotherapy and their proposed neural mechanisms	

(*Continued*)

SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Anderson FS, Kunin-Batson AS, Perkins JL, et al. White versus gray matter function as seen on neuropsychological testing following bone marrow transplant for acute leukemia in childhood. Neuropsychiatr Dis Treat. 2008;4:283-8.	4a	N = 36 children treated for childhood leukemia with hematopoietic stem cell transplant	Previous studies have not demonstrated a discrepancy between white and gray matter function	• White matter damage is responsible for the more subtle neurocognitive late effects resulting from treatment for childhood leukemia • A gray matter composite was calculated as a mean of the total score for trials 1–5 on the California Verbal Learning Test – Children's version (CVLT-C) and the Verbal Intellectual Quotient (VIQ) on the Wechsler Abbreviated Scale of Intelligence (WASI). The white matter composite score was calculated as an average of a Conners' Continuous Performance Test (CPT) composite (an average of the omissions, response time and variability scores, created so as to not weight one test more heavily than the other) and the Block Design score from the WASI.
Anderson JF, Rosenfeld JV. Long-term cognitive outcome after transcallosal resection of hypothalamic hamartoma in older adolescents and adults with gelastic seizures. Epilepsy Behav. 2010;18:81-7.	4b	6 patients who underwent TAIF surgical HH resection in adolescence or young adulthood	To describe neurocognitive outcome after HH resection with the transcallosal anterior interforniceal (TAIF) approach	• 4/6 patients had pre-op NP testing, all 6 had testing post-op • 1 of these patients demonstrated improvement at post-op testing • Perception/visual-spatial function improved (>1SD) from below average per-op performance • Memory was the only neurocognitive domain in which postoperative deterioration was evident. Deterioration was most commonly seen in the verbal memory domain. 3 of 4 declined on this dimension. • This article is not particularly helpful.
Annett RD, Hile S, Bedrick E, et al. Neuropsychological functioning of children treated for acute lymphoblastic leukemia: impact of whole brain radiation therapy; Psychooncology. 2015;24:181-9.	2	N = 188 children, ages 4-21 years at enrollment, were assessed with standardized neuropsychological tests at 9, 21 and 48 months after diagnosis with intermediate risk ALL	Prospectively determine the impact of whole brain radiotherapy in children being treated for ALL on a cooperative group study	• A trajectory of decline in neuropsychological functioning, specifically in a child's verbal IQ was observed.
Armstrong GT, Conklin HM, Huang S, et al. Survival and long-term health and cognitive outcomes after low-grade glioma.Neuro Oncol. 2011;13:223-34.	4a	182 5-year survivors of low-grade glioma	Examine exposure-specific characterization and long-term morbidity for children with low-grade glioma	• 34% had an intelligence quotient below average (<85), which was associated with younger age at diagnosis, epilepsy, and shunt placement.
Armstrong GT, Jain N, Liu W, et al. Region-specific radiotherapy and neuropsychological outcomes in adult survivors of childhood CNS malignancies. Neuro Oncol. 2010;12:1173-86.	4a	818 adult survivors of childhood CNS tumors	To examine associations between region-specific radiation dose and self-reported neurocognitive and HRQOL outcomes	• Irradiation in the temporal region (but not other regions) was significantly associated with Memory problems, with a dose-response effect. • Temporal region radiation at all levels was associated with physical limitations; poor general health at ≥ 30 Gy, and poor social functioning at ≥ 50 Gy. • Radiation of the frontal region was associated with physical limitations and poor general health • Poor executive functions were not associated with frontal lobe radiation, but relatively small n in this category who received high radiation • MB/PNET survivors reported more difficulties with task efficiency and organization than survivors of other tumor types

(*Continued*)

SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Armstrong GT, Liu Q, Yasui Y, et al. Long-term outcomes among adult survivors of childhood central nervous system malignancies in the Childhood Cancer Survivor Study. J Natl Cancer Inst. 2009;101:946-58.	4a	2821 Childhood Cancer Survivor Study participants	Characterizes patterns of late mortality, the long-term risks of subsequent neoplasms and debilitating medical conditions, and sociodemographic outcomes	• Cumulative late mortality at 30 years was 25.8%. • Neurocognitive impairment was high and proportional to radiation dose for specific tumor types.
Armstrong GT, Reddick WE, Petersen RC, et al. Evaluation of memory impairment in aging adult survivors of childhood acute lymphoblastic leukemia treated with cranial radiotherapy. J Natl Cancer Inst. 2013;105:899-907.	4b	264 survivors of childhood acute lymphoblastic leukemia (ALL)	Cross-sectional evaluation of survivors of ALL treated with 18 Gy (n = 127) or 24 Gy (n = 138) CRT	• Survivors who received 24 Gy, but not 18 Gy, CRT had impairment in immediate and delayed memory. • The mean score for long-term narrative memory among survivors who received 24 Gy CRT was equivalent to that for individuals older than 69 years. • Impaired immediate memory was associated with smaller right and left temporal lobe volumes, and impaired delayed memory was associated with thinner parietal and frontal cortices.
Arvidson J, Kihlgren M, Hall C, et al. Neuropsychological functioning after treatment for hematological malignancies in childhood, including bone autologous marrow transplantation. Pediatr Hematol Oncol. 1999;16:9-21.	4b	26 children, 2-10 years after autologous bone marrow transplant for hematological malignancies	Cross-sectional design, assessing global IQ and neuropsychological performance	• Global IQ within normative range • Lower performance on selective tests of attention, memory • Lower age at transplant and longer time since transplant correlated with poorer performance on IQ and attention measures
Ashford J, Schoffstall C, Reddick WE, et al. Attention and working memory abilities in children treated for acute lymphoblastic leukemia. Cancer. 2010;116:4638-45.	4b	97 children with ALL who received risk-directed tx (low, standard/ high)	To examine attention and WM abilities of childhood ALL survivors To examine the unique contribution WM makes to IQ To examine the association between WM, attention, and treatment-related white-matter changes	• Children were tested 2 years after completion of consolidation. • Estimated IQ (Sim/BD) did not differ from pop norms across the sample, or for any risk-group. • Significant differences on digit span task (total, forwards, back) for standard/high risk group compared to normative data reflecting problems with attention and WM. • Low risk and standard/high risk patients all performed poorly on digits backwards, but intact on forward and total DS score. 65% of patients fell at least 1 SD below the mean on DSB • 21% of the variance in EIQ is explained by DSF and DSB. DSB contributed unique variance beyond DSF. • Greater volumes of leukoencephalopathy based on neuro-radiologist ratings were associated with lower scores on TDS across all patients. • WM is sensitive to current treatment regimens despite risk-adapted treatment stratification of patients. • Treatment-induced white matter changes were associated with decreased attention and WM. Those with leukoencephalopathy scored lower on WM and attention tasks. Imaging data was obtained at the end of consolidation therapy.

(*Continued*)

SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Askins MA, Moore BD 3rd. Preventing neurocognitive late effects in childhood cancer survivors. J Child Neurol. 2008;23:1160-71.	7	N/A	To summarize the current efforts and explore the prevention of late effects through rehabilitative strategies, continuation of school, and pharmacotherapy	• Neurocognitive domains more affected by cancer treatments: attention, executive functioning, processing speed, working memory, and ability to learn (adversely affect academic performance). • Risk factors for poor outcomes: young age at treatment, increasing time since treatment (specifically for those who received cranial radiation?), neurological severity in perioperative period, acute sequelae of therapy, genetic polymorphisms. • Prevention efforts: advanced radio/chemotherapy techniques, early educational, cognitive, behavioral, pharmacological interventions (specifics listed in article)
Baron Nelson M, Compton P, Patel SK, et al. Central nervous system injury and neurobiobehavioral function in children with brain tumors: a review of the literature. Cancer Nurs. 2013;36:E31-47.	7	NA	Reviews and consolidates what is known about the effects of cranial radiation and chemotherapy on normal brain tissue and to synthesize that information relative to neurobiobehavioral findings in children with brain tumors	• 70 articles were reviewed, and 40 were chosen for inclusion.
Barrera M, Atenafu E. Cognitive, educational, psychosocial adjustment and quality of life of children who survive hematopoietic SCT and their siblings. Bone Marrow Transplant. 2008;42:15-21.	4a	46 HSCT survivors, age 3-16 years, assessed at 2 years post-SCT, and 33 siblings	Compare survivors to siblings and normative data on cognitive and quality of life outcomes	• Survivors did not differ from siblings in global IQ scores, and all scores were within the average range. • Academic achievement scores also within average range • Survivors obtained lower internalizing scores than siblings by parent report • Survivors obtained lower physical, but not psychosocial quality of life scores
Beebe DW, Ris MD, Armstrong FD, et al. Cognitive and adaptive outcome in low-grade pediatric cerebellar astrocytomas: evidence of diminished cognitive and adaptive functioning in National Collaborative Research Studies (CCG 9891/POG 9130). J Clin Oncol. 2005;23:5198-204.	4b	103 children aged 3 to 18 years with low-grade cerebellar astrocytomas	Assessed whether resected but not irradiated pediatric cerebellar tumors are associated with cognitive and adaptive functioning deficits. Examined the effect of tumor location and medical complications on cognitive and adaptive functioning	• All children demonstrated elevated risk for cognitive and adaptive impairment that was not associated consistently with medical complications. • Tumor location had little effect on cognitive, adaptive, or medical outcome.
Benesch M, Spiegl K, Winter A, et al. A scoring system to quantify late effects in children after treatment for medulloblastoma/ependymoma and its correlation with quality of life and neurocognitive functioning. Childs Nerv Syst. 2009;25:173-81.	4a	23 patients with medulloblastoma or ependymoma; 8 patients with low grade glioma (LGG)	Aim was to quantify the severity of late effects by a simple numerical score (late effects severity score, LESS) in patients who received radiochemotherapy for medulloblastoma or ependymoma	• Patients with medulloblastoma/ependymoma had significantly higher LESS and significantly lower Wechsler Adult Intelligence Scale (WAIS)/Wechsler Intelligence Scales for Children (WISC) scores compared to patients with LGG.

(*Continued*)

SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Brackett J, Krull KR, Scheurer ME, et al. Antioxidant enzyme polymorphisms and neuropsychological outcomes in medulloblastoma survivors: a report from the Childhood Cancer Survivor Study. Neuro Oncol. 2012;14:1018-25.	4a	109 medulloblastoma survivors and 143 siblings	Investigated the role of antioxidant enzyme polymorphisms in moderating psychological or neurocognitive impairment	• Patients <7 years of age at diagnosis displayed more problems with task efficiency and fewer problems with somatic complaints than did patients ≥7 years of age. • Female patients reported more organization problems than did male patients.
Brier MJ, Schwartz LA, Kazak AE. Psychosocial, health-promotion, and neurocognitive interventions for survivors of childhood cancer: a systematic review. Health Psychol. 2015;34:130-48.	7	NA	Systematic review summarizes the efficacy of psychosocial, health behavior, and neurocognitive interventions for survivors of pediatric cancer	• 24 interventions were identified (7 psychosocial, 10 health behavior, and 7 neurocognitive). • 11 were controlled trials, of which 7 achieved medium to large effect sizes.
Brinkman TM, Reddick WE, Luxton J, et al. Cerebral white matter integrity and executive function in adult survivors of childhood medulloblastoma. Neuro Oncol. 2012;14 Suppl 4: iv25-36.	4a	20 adult survivors of medulloblastoma	Examines associations between specific cognitive processes and white matter in long-term adult survivors of medulloblastoma	• Mean full-scale intelligence quotient was nearly 1 SD below the normative mean. • Seventy-five percent of survivors were impaired on at least one measure of executive function. • Radial diffusivity in the frontal lobe of both hemispheres was correlated with shifting attention and cognitive flexibility.
Buizer AI, De Sonneville LM, van den Heuvel-Eibrink MM, et al. Visuomotor control in survivors of childhood acute lymphoblastic leukemia treated with chemotherapy only. J Int Neuropsychol Soc. 2005;11:554-65.	4c	34 ALL, 38 Wilms Tumor(non-CNS directed chemotherapy), 151 healthy Control	To analyze the effects of chemotherapy on various levels of visuomotor control in survivors of childhood ALL treated without cranial irradiation, and to identify risk factors for possible deficits	• No significant main or interaction effects on the measures of baseline speed, tracking accuracy and tracking stability and effect sizes were small for all groups. • Differences did emerge for measures of pursuit accuracy and stability between ALL survivors and controls, with significantly worse results for ALL survivors. • Significant risk factors for poorer performance were female gender and a short time since end of treatment, and a trend was found for a young age at diagnosis. • A high cumulative methotrexate dose was an adverse predictive factor in girls. • Chemotherapy-induced central neurotoxicity in childhood ALL is associated with higher order visuomotor control deficits, and that girls appear to be particularly vulnerable.
Buizer AI, de Sonneville LM, van den Heuvel-Eibrink MM, et al. Chemotherapy and attentional dysfunction in survivors of childhood acute lymphoblastic leukemia: effect of treatment intensity. Pediatr Blood Cancer. 2005;45:281-90.	4C	36 with ALL (plus a Wilms tumor control group and a healthy control group)	To determine the long-term effects of CNS-directed chemotherapy on attention and information processing	• Little difference between patients with ALL who received medium dose MTX compared with controls – only differed on one speed/stability measure of the Amsterdam Neuropsychological Task (ANT). • Patients who received HD-MTX performed worse than controls on 3/6 speed/stability measures of the ANT program. • There are subtle deficits in attention and information processing in children treated for ALL, with attentional function predominantly in children receiving intensive therapy (including HD-MTX). • No evidence for attention differences between children treated with dexamethasone versus prednisone.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Butler RW, Copeland DR. Attentional processes and their remediation in children treated for cancer: a literature review and the development of a therapeutic approach. J Int Neuropsychol Soc. 2002;8:115-24.	4a	31 off-therapy cancer survivors	develop an innovative, psychologically based outpatient rehabilitation program that would improve dysfunctional attentional processes and associated neuropsychological deficits. The characteristics of this program and a pilot study of its effectiveness are described	• 21 completed the cognitive remediation program (CRP) and 10 served as comparisons. • CRP group exhibited statistically significant improvement on all attentional measures. • Neither group demonstrated statistically significant changes on the arithmetic achievement test.
Butler RW, Copeland DR, Fairclough DL, et al. A multicenter, randomized clinical trial of a cognitive remediation program for childhood survivors of a pediatric malignancy. J Consult Clin Psychol. 2008;76:367-78.	RCT	N = 161 (2/3 randomized to the intervention)	To evaluate the Cognitive Remediation Program (CRP) in a randomized control fashion The intervention consists of 20 two hour sessions over 4-5 months	• In the intervention arms, there was parent report of improved attention and statistically significant increases in academic achievement. • There were no statistically significant differences in neurocognitive functioning, even though trends were • Supportive of mild gains in neuropsychological development. • Of note, only 60% of participants in the CRP arm completed the entire regimen. • Effect sizes were modest but were comparable with those for other clinical trials of brain injury rehabilitation and for psychological interventions in general.
Butler RW, Haser JK. Neurocognitive effects of treatment for childhood cancer. Ment Retard Dev Disabil Res Rev. 2006;12:184-91.	7	NA	Reviews research on the neuropsychological effects that central nervous system (CNS) cancer treatments have on the cognitive abilities of children and adolescents	
Butler RW, Mulhern RK. Neurocognitive interventions for children and adolescents surviving cancer. J Pediatr Psychol. 2005;30:65-78.	7	NA	Reviews interventions for the neuropsychological late effects associated with the treatment of acute lymphoblastic leukemia (ALL) and malignant brain tumors	
Butler RW, Sahler OJ, Askins MA, et al. Interventions to improve neuropsychological functioning in childhood cancer survivors. Dev Disabil Res Rev. 2008;14:251-8.	7	7	To review behavioral or rehabilitative as well as pharmacologic interventions to improve neuropsychological functioning in cancer survivors	• Younger age at treatment and female gender discussed as risk factors for neuropsychological dysfunction. • Focus on interventions included stimulant therapy and cognitive remediation, with discussion regarding the complex and multi-disciplinary nature of successful interventions as well as the needs of most survivors beyond what the school system can handle.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Callu D, Viguier D, Laroussinie F, et al. Cognitive and academic outcome after benign or malignant cerebellar tumor in children. Cogn Behav Neurol. 2009;22: 270-78.	4b	20 children with cerebellar MT 19 with cerebellar benign tumor	To examine the impact of the precise tumor location on motor, cognitive, and psychological difficulties after resection of cerebellar benign tumor (BT) or malignant tumor (MT)	• All children underwent surgical resection. MT also had chemo and/or radiation. • Paris study. Examined at least 6 months after the end of treatment. • Children with MT showed more cognitive and motor difficulties than BT. • Extent of the DN lesion was related to cognitive and motor impairment. • No behavioral or emotional changes were reported by teachers. • All 3 children who had cerebellar mutism post-op had a DN lesion, but not all children with DN lesion had a history of cerebellar mutism (but this may be underreported). • 73% of parents rated their child as having a learning difficulty. Parents rated more memory impairment in those with MT than BT. • Teachers noted those with MT were underactive, moved more slowly. • High correlation between motor and cognitive difficulties. • Signs of cerebellar syndrome at simple clinical exam should lead to more thorough neuropsych assessment.
Campbell LK, Scaduto M, Sharp W, et al. A meta-analysis of the neurocognitive sequelae of treatment for childhood acute lymphocytic leukemia. Pediatr Blood Cancer. 2007;49:65-73.	1	28 empirical studies published between 1980 and 2004 comparing patients treated for ALL with CNS-directed therapy as compared to control groups of healthy peers or siblings and groups of children treated for solid tumors or other chronic illnesses without CNS prophylaxis	Review the long-term general and specific neurocognitive effects of treatment for ALL, particularly CNS prophylaxis	• There is a relative decline in functioning for children treated for ALL when compared to all control groups combined. • All 13 mean effect sizes that extracted across the nine evaluated neurocognitive domains were in the negative direction (g = -0.34 to -0.71). • There were no differences in direction or magnitude of neurocognitive decline for patients treated for ALL when separate analyses were conducted for comparisons for ALL treated groups with healthy peers and siblings and those with groups of children treated for solid tumors or with other chronic illnesses. • Clinically significant deficits in attention and speed of information processing as well as in areas of executive functioning were identified in the ALL treated group as compared to the control groups. • ALL groups that received both cranial irradiation and intrathecal chemotherapy performed significantly more poorly for overall intellectual functioning than those who received intrathecal chemotherapy alone. • The study did not support the conclusion that patients treated with intrathecal chemotherapy without CRT are at no risk for long-term treatment-related neurocognitive effects. • Analyses of the effect of age at diagnosis (<5 yrs age vs. >/= 5yrs age) and time elapsed since end of treatment (< 5 yrs and >/= 5yrs) on neurocognitive outcomes, were inconclusive.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Caron JE, Krull KR, Hockenberry M, et al. Oxidative stress and executive function in children receiving chemotherapy for acute lymphoblastic leukemia. Pediatr Blood Cancer. 2009;53:551-6.	4a	88 children with newly diagnosed ALL	To investigate the association between markers of oxidative stress (following induction and consolidation phases of chemo) and difficulties with exec fx at post-consolidation and the end of therapy	• Oxidized PC levels significantly increased from dx to post-induction and from dx to post-consolidation • Overall group performance on measures of executive function were elevated though patients did not significantly differ from norms. • Pt distribution of scores was more positively skewed with greater variability than the norm, suggesting subset of patients more adversely affected. • Increased oxidative stress was associated with poorer WM, poorer organization of materials, and attention problems at the end of therapy. • Correlations suggest increased measures of oxidative stress were associated with greater executive dysfunction. • Younger age at dx was associated with higher oxidized PC reactivity at consolidation and with poorer executive functions. • Females had poorer WM at the end of tx than males. • Oxidative stress from MTX treatment appears associated with poorer exec functions in children at the end of chemo. Unclear whether these deficits develop into LT effects or remit over time. • Oxidative stress is one mechanism responsible for difficulties with executive function.
Castellino SM, Tooze JA, Flowers L, et al. The Peabody picture vocabulary test as a pre-screening tool for global cognitive functioning in childhood brain tumor survivors. J Neurooncol. 2011;104:559-63.	4b	13 pediatric BT survivors who received greater than 23.4 Gy CRT	To determine the utility of the PPVT-III as a screening tool in evaluating eligibility for a pilot intervention study among childhood BT survivors. Determine if the test is useful in determining whether the child has adequate level of cognitive capacity to understand and complete self-report measures and follow instructions in other study assessments	• The test was administered with ease within 20 minutes. • Correlation of PPVT-III with the WASI was .90 for FSIQ, .89 VIQ and .75 for PIQ. • The PPVT-III is a feasible screening tool and an indicator of minimal global intelligence in pediatric BT survivors. Can be used as a way to determine whether patients can reliably and validly respond and participate with NP testing or PROs are being used.
Castellino SM, Tooze JA, Flowers L, et al. Toxicity and efficacy of the acetylcholinesterase (AChe) inhibitor donepezil in childhood brain tumor survivors: a pilot study. Pediatr Blood Cancer. 2012;59:540-7.	4	11 childhood brain tumor survivors	To explore the impact of donepezil on executive function in survivors of childhood brain tumors. To report feasibility, tolerance, and impact of donepezil on executive function and other neurocognitive domains	• Significant improvement of executive function (D-KEFS Tower task). After drug washout period, score dropped. Medium effect on Color/Word Interference Inhibition. Medium effect in visual memory. Small effect in Number/Letter Memory. Non-significant but medium effects in detectability and overall response style scores of CPT-II. • Medium effect on plan/organize, working memory, and emotional control by parent report (BRIEF); small non-significant improvement in global executive function. 54% requested re-initiation of drug post-study completion based on perceived benefit.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Castellino SM, Ullrich NJ, Whelen MJ, et al. Developing interventions for cancer-related cognitive dysfunction in childhood cancer survivors. J Natl Cancer Inst. 2014;106. pii: dju186.	7	NA	Reviews epidemiology, pathophysiology and assessment of cancer-related cognitive dysfunction, the impact of treatment changes for prevention, and the broad strategies for educational and pharmacological interventions to remediate established cognitive dysfunction following childhood cancer	
Catsman-Berrevoets CE, Aarsen FK. The spectrum of neurobehavioral deficits in the posterior fossa syndrome in children after cerebellar tumour surgery. Cortex. 2010;46:933-46.	4b	148 children with a cerebellar tumor admitted to a single center in the Netherlands	To assess children with cerebellar tumor for posterior fossa syndrome	• 41 children developed PFS after cerebellar tumor surgery and were prospectively followed to examine clinical features • 24% of their cohort developed PFS, consistent with incidence reported in other studies. • A spectrum of symptoms of PFS were reported: transient mutism without neurobehavioral symptoms (n = 2), mutism with severe behavior symptoms of longer duration (n = 34, 83% of sample) and patients with characteristic behavior symptoms but without mutism (n = 5, 12%). • Hypoperfusion on SPECT was present at the tumor resection site bilaterally in the center of the cerebellum (deep cerebellar nuclei) for all children with PFS and mutism. • Children without PFS or with PFS but not mute showed less severe or unilateral perfusion abnormalities of the central cerebellar region. • Correlations were found between duration of mutism and severity of neurological symptoms, severity of SPECT abnormalities of the left temporal lobe, the left and right basal nuclei, and the right frontal lobe.
Challinor J, Miaskowski C, Moore I, et al. Review of research studies that evaluated the impact of treatment for childhood cancers on neurocognition and behavioral and social competence: nursing implications. J Soc Pediatr Nurs. 2000;5:57-74.	7	NA	Reviews and critiques research studies that evaluated the impact of treatment for childhood cancers	• Implications for nursing practice are discussed.
Charalambides C, Dinopoulos A, Sgouros S. Neuropsychological sequelae and quality of life following treatment of posterior fossa ependymomas in children. Childs Nerv Syst. 2009;25:1313-20.	7	N/A	This review article discusses cerebellar mutism, the cerebellar cognitive affective syndrome, the LT NP and behavioral sequelae of posterior fossa ependymomas in children and the role of treatment in outcome	• The cerebellum is not only involved in motor functions, but non-motor functions such as language, emotions, and planning. • Children with brain tumors are at risk for NP impairment and poor QOL. • Early identification and management of NP deficits should be part of the treatment plan if the best outcome is to be achieved.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Cheung YT, Krull KR. Neurocognitive outcomes in long-term survivors of childhood acute lymphoblastic leukemia treated on contemporary treatment protocols: A systematic review. Neurosci Biobehav Rev. 2015;53:108-120.	1	NA	Evaluates the persistence of neurocognitive deficits in long-term survivors of pediatric ALL who were treated with contemporary chemotherapy-only protocols	• Survivors who received chemotherapy treatment still suffered from apparent cognitive impairment, particularly in the attention and executive function domains.
Chiou SS, Jang RC, Liao YM, et al. Health-related quality of life and cognitive outcomes among child and adolescent survivors of leukemia. Support Care Cancer. 2010;18:1581-7.	4c	32 adolescent ALL survivors, 154 community controls, 30 siblings	To examine the QOL and cognitive outcomes of adolescents with ALL, who were in remission for at least 3 years and did not undergo transplant and were less than 18 at the time of study To document QOL and cognitive outcomes in a single-institution Taiwanese sample	• Parent report of HRQOL (CHQ-PF) were significantly lower than community control group in physical summary score, psychosocial summary score, mental health, self-esteem, and general health perception. Survivors also lower than siblings in physical summary score, psychosocial summary score and most subscales. • No associations between QOL scores and time since diagnosis, age at diagnosis, current age, total hospitalization days, and IT MTX dose. IQ score was associated with Phys Summary score. • 85% of survivors had EIQ above 70 • 18/32 survivors underwent more detailed NP testing. 27.5% of these 18 had impairment in one or more of the seven domains assessed (impairment defined as below the mean by 2 SD or more).
Cheung LL, Wakefield CE, Ellis SJ, et al. Neuropsychology reports for childhood brain tumor survivors: implementation of recommendations at home and school. Pediatr Blood Cancer. 2014;61:1080-7.	4a	25 semi-structured interviews with with 17 parents	Explored parent and teacher understanding of neuropsychology reports, implementation rates for recommendations and their perceived effectiveness. Barriers to implementation were investigated	• The majority of parents and teachers had a sound understanding of the report. Implementation of recommendations at home and school was 47% and 41%, respectively
Clanton NR, Klosky JL, Li C, et al. Fatigue, vitality, sleep, and neurocognitive functioning in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Cancer. 2011;117:2559-68.	4a	1426 survivors from the Childhood Cancer Survivor Study	Association between risk for fatigue, sleep problems, and neurocognitive impairment in adult survivors is reported	• Neurocognitive impairment was identified in >20% of survivors, using sibling-based norms for comparison. • Multivariate logistic regression models revealed that fatigue, daytime sleepiness, poor sleep quality, and decreased vitality were all associated with impaired task efficiency.
Cole PD, Finkelstein Y, Stevenson KE, et al. Polymorphisms in Genes Related to Oxidative Stress Are Associated With Inferior Cognitive Function After Therapy for Childhood Acute Lymphoblastic Leukemia. J Clin Oncol. 2015 May 18. pii: JCO.2014.59.0273. [Epub ahead of print]	4a	350 pediatric leukemia survivors	Tested whether interpatient variability in neurocognitive outcomes can be explained by polymorphisms in candidate genes conferring susceptibility to neurocognitive decline	• Inferior cognitive or behavioral outcomes were associated with polymorphisms in three genes related to oxidative stress and/or neuroinflammation: NOS3 (IQ, Q = 0.008; Vocabulary Q = 0.011; Matrix Reasoning Q = 0.008), SLCO2A1 (IQ Q = 0.043; Digit Span Q = 0.006; Block Design Q = 0.076), and COMT (Behavioral Assessment System for Children-2 Attention Q = 0.080; and Hyperactivity Q = 0.084).

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Pediatr Blood Cancer DOI 10.1002/pbc

SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Conklin HM, Ashford JM, Di Pinto M, et al. Computerized assessment of cognitive late effects among adolescent brain tumor survivors.J Neurooncol. 2013;113:333-40.	4a	24 childhood brain tumor (BT) survivors treated with conformal radiation therapy (mean age 15.7 ± 1.6; mean age at irradiation 9.8 ± 2.5), twenty solid tumor (ST) survivors treated without CNS-directed therapy (mean age 16.2 ± 1.8) and twenty healthy siblings (mean age 15.1 ± 1.6 years)	Using a computerized assessment of neuropsychological functions (ImPACT), assess children with brain tumors, solid tumors and healthy siblings	• Group differences on measures of recognition memory, spatial working memory, processing speed and reaction time, with BT survivors performing significantly worse than ST survivors and siblings. • Pearson correlation coefficients revealed significant associations between ImPACT memory tasks and computerized forced choice recognition tasks. • Multiple surgical resections, hydrocephalus and CSF shunt placement most consistently predicted worse ImPACT performance using linear mixed models. • ImPACT demonstrated sensitivity to cognitive late effects experienced by some BT survivors with clinical predictors of performance consistent with the pediatric oncology literature. • Correlations with measures of similar constructs provide evidence for convergent validity.
Conklin HM, Ashford JM, Howarth RA, et al. Working memory performance among childhood brain tumor survivors.J Int Neuropsychol Soc. 2012;18:996-1005.	4b	50 childhood brain tumor survivors; 40 solid tumor; and 40 sibling controls	Evaluated the performance of childhood brain tumor survivors treated with conformal radiation therapy, solid tumor survivors who had not received central nervous system (CNS) -directed therapy, and healthy sibling controls on measures of working memory	• Brain tumor survivors were impaired on both traditional and experimental measures of working memory. • Performance on working memory measures correlated with intellectual functioning.
Conklin HM, Helton S, Ashford J, et al. Predicting methylphenidate response in long-term survivors of childhood cancer: a randomized, double-blind, placebo-controlled, crossover trial. J Pediatr Psychol. 2010; 35:144-55.	2	3-week double-blind crossover trial consisting of placebo, low dose, and moderate dose MPH 106 (51 BT and 55 ALL)	To examine the MPH response rate among survivors and to identify predictors of positive MPH response	• Weekly teacher and parent reports on the Conners Rating scales were gathered. • Following MPH dose, 45.28% of the sample was classified as responders. • Findings revealed that more problems endorsed prior to the medication trial on parent and teacher ratings were predictive of positive medication response. • MPH significantly reduces attention problems in a subset of survivors. • Parent and teacher ratings may assist in identying children most likely to respond to MPH so prescribing may be optimally targeted.
Conklin HM, Khan RB, Reddick WE, et al. Acute neurocognitive response to methylphenidate among survivors of childhood cancer: a randomized, double-blind, cross-over trial. J Pediatr Psychol. 2007;32:1127-39.	2	(N = 122) completed a two-day, in-clinic, double-blind, cross-over trial during which they received MPH (0.60 mg/kg of body weight) and placebo that were randomized in administration order across participants	To investigate the acute efficacy and adverse side effects of methylphenidate (MPH) among survivors of childhood **cancer** [acute lymphoblastic leukemia (ALL) or brain tumor (BT)] with learning impairments	• A significant MPH versus placebo effect was revealed on a measure of attention, cognitive flexibility, and processing speed (Stroop Word-Color Association Test). • Male gender, older age at treatment, and higher intelligence were predictive of better medication response. No significant differences were found for number or severity of adverse side effects as a function of active medication.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Conklin HM, Krull KR, Reddick WE, et al. Cognitive outcomes following contemporary treatment without cranial irradiation for childhood acute lymphoblastic leukemia. J Natl Cancer Inst. 2012;104:1386-95.	4a	243 children treated with chemotherapy only for ALL	To examine neurocognitive functioning in patients enrolled on the St Jude ALL Total Therapy Study XV, which omitted prophylactic cranial irradiation in all patients, 120 weeks after completion of consolidation therapy using a comprehensive cognitive battery	• ALL group had a statistically significantly higher risk for below-average performance on a measure of sustained attention but not on measures of intellectual functioning, academic skills, or memory compared to expected rate based of the normative sample. • Patients given higher intensity chemotherapy were at greater risk for below-average performance compared with those given lower intensity therapy on measures of processing speed and academic abilities and had higher parent-reported hyperactivity and learning problems.
Conklin HM, Lawford J, Jasper BW, et al. Side effects of methylphenidate in childhood cancer survivors: a randomized placebo-controlled trial. Pediatrics. 2009;124:226-33.	4b	103 survivors and 49 sibling healthy comparison group	To examine side effects of MPH and identify predictors of higher adverse effect levels	• Higher side effects endorsed when taking moderate dose compared with placebo or low dose. Female gender and lower IQ were associated with higher adverse effect levels.
Conklin HM, Reddick WE, Ashford J, et al. Long-term efficacy of methylphenidate in enhancing attention regulation, social skills, and academic abilities of childhood cancer survivors. J Clin Oncol. 2010;28:4465-72.	4b	Examined 35 BT and 33 ALL on neurocognitive measures compared to 31 BT and 23 ALL not administered MPH	To evaluate the long-term efficacy of MPH in childhood cancer survivors after 12 months of use	• Group treated with MPH showed sig improvement on CPT indices, and parent ratings of social skills (SSRS) and on the CBCL. • Cancer control group showed improvement only on SSRS and Conners Parent Rating Scales indices. • No significant improvement on the academic measure in either group.
Cool VA. Long-term neuropsychological risks in pediatric bone marrow transplantation: what do we know? Bone Marrow Transplant. 1996;18:S45-9.	4a	Cohort of 76 children assessed pre-SCT; variable numbers assessed at subsequent time points through 4 years-post-SCT	Examine the effects of BMT on the neuropsychological functioning of children. Standardized measures of IQ, academic achievement, and specific neuropsychological functions	• At pre-SCT evaluation, some children already showing deficits, related to prior CNS therapy. • At 1-yr post-SCT global IQ and achievement stable. • Trends in decline over time, but not statistically significant. • Data presented insufficient to appreciate longitudinal findings.
Copeland DR, Moore BD 3rd, Francis DJ, et al. Neuropsychologic effects of chemotherapy on children with cancer: A longitudinal study. J Clin Oncol. 1996;14:2826-35.	4a	99 children received no cranial radiation therapy (CRT) completed four annual neuropsychologic assessments. 51 of the sample were examined 5-11 years after diagnosis	Assess effects of chemotherapy on children's long-term neuropsychologic status	• Effects of chemotherapy in the absence of CRT appear to be slight. • Patients who received ITC and intravenous (IV) methotrexate declined slightly on perceptual-motor skills, but were still well within the normal range. • Both groups, regardless of treatment, declined on academic achievement tests, although not to a statistically significant degree. • Age effects were found on performance IQ (PIQ) and perceptual-motor skills. • Socioeconomic status (SES) correlated with a large number of variables. • Sex effects were not significant.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Daly BP, Brown RT. Scholarly literature review: management of neurocognitive late effects with stimulant medication. J Pediatr Psychol. 2007;32:1111-26.	7	NA	Examine the extant literature on stimulant drug therapy for survivors of childhood cancer during the late-effects period	• 4 studies were found that have examined the effects of stimulant medication on the cognitive toxicities of childhood survivors of cancer during the late-effects period and only two of these investigations were controlled clinical trials. • Findings suggest efficacy of the stimulants on parent and teacher ratings of attention and putative tasks of attention and executive functioning
Davis EE, Pitchford NJ, Jaspan T, et al. Development of cognitive and motor function following cerebellar tumour injury sustained in early childhood. Cortex. 2010;46: 919-32.	4c	15 children with cerebellar injury (ages 4-14) following tumor dx at <5 years; 242 control children ages 4-11	To examine the relationship between cognitive and motor skills across development and establish the possible mediating role of the cerebellum in this relationship Investigate prognostic factors that might influence performance within the cerebellar patient group	• KABC-II and BOT-2 were outcomes of interest (UK Study) • Strong positive association between cognitive and motor skills from early to middle childhood, suggesting that cognitive and motor skills seem to develop in parallel. • The strength of the relationship between cognitive and motor development does not appear to be affected by cerebellar tumor – rather there was a "clear pattern of developmental delay" for both motor and cognitive development in the 15 children who were status post cerebellar tumor. • Because of small sample size, they really cannot draw sound conclusions about the impact of potential moderating variables (age at diagnosis, treatment, hydrocephalus, tumor location) on outcome. The authors assert that children with astrocytoma and surgery only (n = 6) performed better than the other patients in the sample. Age at diagnosis was associated with cognitive performance to some degree (r = .6 visual processing).
Dennis JM, Rosen R, Patel SK. Willingness to participate in a parental training intervention to reduce neurocognitive late effects among Latino parents of childhood cancer survivors. J Cancer Educ. 2015;30:37-44.	4a	73 Latino caregivers of school-age children who are survivors of brain tumor or leukemia	Examines correlates of Spanish-speaking Latino parents' interest for participation in an educational intervention to improve learning and school success in children with cancer-related cognitive and behavioral late effects	• The majority of parents expressed interest in participating in the proposed 8-week intervention, with over 90% indicating interest in learning more about improving grades, making learning more exciting, being a role model, and the impact of cancer on memory.
de Ruiter MA, Schouten-Van Meeteren AY, van Mourik R, et al. Neurofeedback to improve neurocognitive functioning of children treated for a brain tumor: design of a randomized controlled double-blind trial. BMC Cancer. 2012;12:581.	6	NA	Describes the protocol of the PRISMA study, a randomized controlled trial to investigate the efficacy of neurofeedback to improve neurocognitive functioning in children treated for a brain tumor	
de Ruiter MA,Van Mourik R, Schouten-Van Meeteren AY, et al. Neurocognitive consequences of a paediatric brain tumour and its treatment: a meta-analysis. Dev Med Child Neurol. 2013;55:408-17.	1	29 studies	Meta-analysis and systematic review of studies into intellectual and attentional functioning of paediatric brain tumour survivors (PBTS) as assessed by two widely used measures: the Wechsler Intelligence Scale for Children (3rd edition; WISC-III) and the Conners' Continuous Performance Test (CPT)	• Twenty-nine studies were included: 22 reported on the WISC-III in 710 PBTS and seven on CPT results in 372 PBTS. • PBTS performed below average (ps < 0.001) on Full-scale IQ (Cohen's d = -0.79), Performance IQ (d = -0.90), and Verbal IQ (d = -0.54). • PBTS committed more errors of omission than the norm(d = 0.82, p < 0.001); no differences were found for mean hit reaction time and errors of commission. • Cranial radiotherapy, chemotherapy, and longer time since diagnosis were associated with lower WISC-III scores (ps < 0.05).

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
De Smet HJ, Baillieux H, Wackenier P, et al. Long-term cognitive deficits following posterior fossa tumor resection: a neuropsychological and functional neuroimaging follow-up study. Neuropsychology. 2009;23:694-704.	4b	5 boys status post resection of posterior fossa tumors	To describe acute and LT linguistic, cognitive, and affective symptoms of 5 children who underwent PF tumor resection by means of an extensive NP test battery	• Case studies of 5 right-handed boys following PF tumor resection, presented with conspicuous speech and language disturbances, cognitive deficits and behavior alterations. After a short postoperative period of normal functioning, 4 patients developed mutism, followed by dysarthria and one patient presented with severe word finding difficulties and poor expressive language. • 4 patients had severe frontal-like behavior and affective disturbance, such as apathy, inhibition, infantile and regressive behavior, loss of facial expression, withdrawal in the immediate postop phase.
			To test the pathophysiological hypothesis of a diachisis phenomenon underlying PFS	• NP testing showed frontal/exec deficits, concentration difficulty and visual-spatial problems. All needed intensive cog rehab therapy. 4/5 enrolled in special education. • Cognitive cerebellar affective syndrome may be viewed as a LT consequence of PFS. • Quantified ECD-SPECT in the immediate postop phase revealed that cerebellocerebral diaschisis might play a role in transient cerebellar mutism in PFS.
Di Pinto M, Conklin HM, Li C, et al. Investigating verbal and visual auditory learning after conformal radiation therapy for childhood ependymoma. Int J Radiat Oncol Biol Phys. 2010;77:1002-8.	4a	71 patients with localized ependymoma enrolled in a Phase II trial of CRT. All patients received CRT over 6-weeks with dose fractionated to 1.8 Gy per day. Total dose ranged from 54 to 59.4 Gy	To determine whether children with localized ependymoma experience a decline in verbal or visual auditory learning after CRT To investigate the impact of age and other clinical factors on learning before and after treatment	• Mean scores on CVLT-C and VAL were average at start of CRT. No evidence of decrease in CVLT-C and VAL scores over time following CRT. • Older children had higher CVLT-C scores 5 years after tx than younger children. • Patients treated with "smaller than conventional" volumes using CRT do not exhibit longitudinal decline in verbal or visual auditory learning after tx. • Older children displayed more rapid rate of learning over time than younger children on CVLT-C but not the VAL. Older children had better verbal learning at baseline and more rapid improvement in verbal learning over time and higher verbal learning scores 5 years post CRT than younger children. • Multiple tumor resections and CSF shunts had worse verbal and VAL learning at baseline, but did not predict differences 5 years after tx. • Supratentorial tumor location was not a risk factor for learning outcome. • Trend for pre-CRT chemo to be associated with slower rates of VAL after treatment. • VAL was mores susceptible to a greater number of risk factors than verbal learning (i.e., pre-CRT chemo, more surgeries), and this may help explain why children with localized ependymoma are at greater risk for reading difficulty. • Obtaining baseline testing is necessary. Learning scores were typically within the average range despite significant subgroup differences. Modest yet significant effects would not have been detected without careful baseline measurement for comparison. • Younger children, those receiving pre-CRT chemo, and those with more perioperative complications may be at increased risk for learning difficulty.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Di Pinto M, Conklin HM, Li C, et al. Learning and memory following conformal radiation therapy for pediatric craniopharyngioma and low-grade glioma.Int J Radiat Oncol Biol Phys. 2012;84:e363-9.	4b	57 children with LGG and 44 children with craniopharyngioma	Longitudinal examination of whether children with low-grade glioma (LGG) or craniopharyngioma had impaired learning and memory after conformal radiation therapy (CRT)	• No decline in learning scores after CRT was observed when patients were grouped by diagnosis. • For children with LGG, chemotherapy before CRT did not provide a protective effect on learning. • Multiple regression analyses, which accounted for age and tumor volume and location, found that children treated with chemotherapy before CRT were at greater risk of decline on learning measures than those treated with CRT alone. • Variables predictive of learning and memory decline included hydrocephalus, shunt insertion, younger age at time of treatment, female gender, and pre-CRT chemotherapy.
Di Rocco C, Chieffo D, Pettorini BL, et al. Preoperative and postoperative neurological, neuropsychological and behavioral impairment in children with posterior cranial fossa astrocytomas and medulloblastomas: the role of the tumor and the impact of the surgical treatment. Childs Nerv Syst. 2010;26:1173-88.	4a	41 children with posterior fossa tumors (either MBL or Astrocytoma) Neuropsych testing done before surgery & after surgery (mean 2.5mos after)	Prospectively investigate if a correlation exists between per- and postoperative neurological conditions, neuroradiological/ intraoperative findings and results of complete neuropsychological evaluation in children with PF MBL and astrocytomas	• Preoperative occulomotor impairment associated with verbal fluency deficits and imagery disorders. • Presence of preoperative ataxia/dysmetria correlated to attention dysfunction (planning in particular). • IQ impairment correlated to tumor infiltration of the brainstem, severe hydrocephalus at diagnosis, and medulloblastoma histology. • Infiltration of the dentate nuclei by tumor associated with linguistic processing deficits. • Procedural memory and imagery disorders associated with the severity of hydrocephalus, infiltration of the brain stem, and medulloblastoma histology. • Variable degrees of neuropsychological impairment might be present at diagnosis. • Tumor removal may be by an improvement in the defective performances in a significant proportion of cases.
Droit-Volet S, Zélanti PS, Dellatolas G, et al. Time perception in children treated for a cerebellar medulloblastoma. Res Dev Disabil. 2013; 34:480–94.	4b	31 children treated by surgery for a malignant tumor in the cerebellum & 31 control children M age = 10 (range 5-14 years)	Investigate temporal abilities in children treated by surgery for a malignant tumor in the cerebellum and controls	• No significant difference in performance between the children with or without cerebellar lesions in the temporal discrimination task. • Children with cerebellar lesions reproduced longer and more variable durations than the other children, but only for the short stimulus durations. • Hierarchical regression analysis revealed that the best predictor of variance in temporal performance was a significantly lower processing speed in children with cerebellar lesions in comparison to their controls.
Edelmann MN, Krull KR, Liu W, et al. Diffusion tensor imaging and neurocognition in survivors of childhood acute lymphoblastic leukaemia. Brain. 2014;137:2973-83.	4b	Survivors of ALL treated with chemotherapy (N = 36) or radiotherapy (N = 39) were compared with healthy controls (N = 23)	Cross sectional comparison of neurocognitive function and brain morphology in long-term adult survivors of childhood acute lymphoblastic leukemia	• Survivors treated with chemotherapy alone had higher fractional anisotropy in fiber tracts within the left ($P < 0.05$), but not in the right, hemisphere when compared to controls. • Survivors of acute lymphoblastic leukemia, regardless of treatment, had a lower ratio of white matter to intracranial volume in frontal and temporal lobes ($P < 0.05$) compared with control subjects. • Survivors of acute lymphoblastic leukemia treated with chemotherapy alone performed worse in processing speed ($P < 0.001$), verbal selective reminding ($P = 0.01$), and academics ($P < 0.05$) compared to population norms and performed better than survivors treated with cranial radiation therapy on verbal selective reminding ($P = 0.02$), processing speed ($P = 0.05$) and memory span ($P = 0.009$).

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Edelmann MN, Ogg RJ, Scoggins MA, et al. Dexamethasone exposure and memory function in adult survivors of childhood acute lymphoblastic leukemia: A report from the SJLIFE cohort. Pediatr Blood Cancer. 2013;60:1778-84.	4a	38 adult survivors	Investigates memory networks in survivors of childhood ALL treated with dexamethasone or prednisone	• Survivors treated with dexamethasone demonstrated lower performance on multiple memory-dependent measures, including story memory and word recognition, compared to survivors treated with only prednisone.
Edelstein K, D'agostino N, Bernstein LJ, et al. Long-term neurocognitive outcomes in young adult survivors of childhood acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2011;33:450-8.	4a	24 adult survivors of childhood acute lymphoblastic leukemia (ALL)	Aims to explore long-term neurocognitive outcomes in adult survivors of childhood ALL, and to identify measures sensitive to neurotoxicity in long-term survivors	• Younger age at diagnosis and longer time since diagnosis were associated with lower scores on a computerized battery that requires speed and accuracy across a number of domains (MicroCog), and other standardized neurocognitive tests. • When compared with population norms, MicroCog indices were below average in survivors diagnosed with ALL before age 5, but only the reasoning/calculation index was below average in survivors diagnosed with ALL after age 5.
Edelstein K, Spiegler BJ, Fung S, et al. Early aging in adult survivors of childhood medulloblastoma: long-term neurocognitive, functional, and physical outcomes. Neuro Oncol. 2011;13:536-45.	4a	20 adults who were treated with surgery and radiotherapy for medulloblastoma during childhood (median age at assessment, 21.9 years; median time since diagnosis, 15.5 years; Data from prior neuropsychological assessments were available for 18 subjects	Little is known about the long-term neurocognitive, functional, and physical outcomes in adult survivors of childhood medulloblastoma	• The group was well below average across multiple neurocognitive domains, and 90% had required accommodations at school for learning disorders. • Longer time since diagnosis, but not age at diagnosis, was associated with continued decline in working memory, a common sign of aging. • Younger age at diagnosis was associated with lower intelligence quotient and academic achievement scores, even many years after treatment had been completed. • The most common health complications in survivors were hearing impairment, second cancers, diabetes, hypertension, and endocrine deficiencies. • Adult survivors of childhood medulloblastoma exhibit signs of early aging regardless of how young they were at diagnosis.
ElAlfy M, Ragab I, Azab I, et al. Neurocognitive outcome and white matter anisotropy in childhood acute lymphoblastic leukemia survivors treated with different protocols. Pediatr Hematol Oncol. 2014;31:194-204.	4a	62 ALL survivors	Assesses the prevalence of neurocognitive dysfunction by psychometric and imaging tools in survivors of childhood ALL, treated with 3 different protocols	• Survivors treated with modified CCG protocol showed a significant decrease in all cognitive tests compared to control; BFM 90 group had a significant lower IQ and longer TMT compared to both control and BFM 83 group and no significant difference was found in results of cognitive tests between BFM 83 and control group.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Ellenberg L, Liu Q, Gioia G, et al. Neurocognitive status in long-term survivors of childhood CNS malignancies: a report from the Childhood Cancer Survivor Study. Neuropsychology. 2009;23:705-17.	4b	802 childhood CNS cancer survivors, 5937 survivors of childhood non-CNS cancer, & 382 non-affected sibs completed the CCSS-Neurocognitive Questionnaire	To examine and quantify neurocognitive functioning and adaptive outcome in adult survivors of childhood CNS malignancies who are 16-34 years from their original diagnosis	• CNS-malignancy survivors reported greater neurocognitive impairment on all CCSS-NCQ factors. • Within the CNS malignancy group, medical complications (hearing deficits, paralysis, cerebrovascular incidents) resulted in a greater likelihood of reported deficits on all 4 factors. • Total or partial brain irradiation and VP shunt placement was associated with a greater likelihood of impaired scores on task efficiency and emotional regulation. • Diagnosis before 2 years of age resulted in less likelihood of reported impairment on the memory factor. • CNS malignancy survivors with more impaired CCSS-NCQ scores demonstrated significantly lower educational attainment, less household income, less full time employment, and fewer marriages. • Survivors of childhood CNS malignancy were found to be at significant risk for neurocognitive impairment that continues to adulthood and is correlated with lower socioeconomic achievement.
Finkelstein-Shechter T, Gassas A, Mabbott D, et al. Atypical teratoid or rhabdoid tumors: improved outcome with high-dose chemotherapy. J Pediatr Hematol Oncol. 2010;32:e182-6.	4a	8 patients with AT/RT: report on 6 who received induction chemotherapy followed by sequential high-dose chemotherapy with autologous stem cell rescue	Retrospectively review their experience in managing AT/RT of the CNS in infants and children less than 4 years of age	• 4 survivors. • All received induction chemotherapy followed by sequential high-dose chemotherapy. • 1 of the 4 survivors received radiotherapy (focal). • 3 underwent formal neuropsychologic testing and 1 a developmental assessment. • All 4 showed either adaptive or cognitive delays at baseline testing or significant cognitive decline with follow-up assessment. • Mean Full Scale IQ for the 3 who had standardized testing was 75.
Gross-King M, Booth-Jones M, Couluris M. Neurocognitive impairment in children treated for cancer: how do we measure cognitive outcomes? J Pediatr Oncol Nurs. 2008;25:227-32.	4a	12 pediatric patients at risk for cognitive dysfunction	Investigates treatment with central nervous system (CNS) stimulants for cognitive changes related to pediatric cancer treatment	• 3 of 12 children tested positive for early neurocognitive deficits using 3 subscales of the Wechsler Intelligence Scale for Children-III (working verbal memory, mental processing speed, and psychomotor speed). • To predict the expected level of performance on WISC-III subscales, IQ was estimated using the Wide Range Achievement Test-3 reading subtest. • Patients were treated with long-acting CNS stimulants and followed up serially using the WISC-III subscales.
Haddy TB, Mosher RB, Reaman GH. Late effects in long-term survivors after treatment for childhood acute leukemia. Clin Pediatr (Phila). 2009;48:601-8.	4a	324 acute leukemia survivors	Report of late effects in childhood cancer survivors seen in the follow-up clinic of a single institution	• One or more adverse events occurred in 74.1% of the survivors. Defective physical growth was most commonly reported, followed by disturbed neurocognitive function, emotional difficulties, cardiac abnormalities, hypertension, osteoporosis/osteopenia, fractures, and second neoplasms.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Hardy KK, Bonner MJ, Willard VW, et al. Hydrocephalus as a possible additional contributor to cognitive outcome in survivors of pediatric medulloblastoma. Psychooncology. 2008;17:1157-61.	4a	Retrospective study on 35 survivors of pediatric medulloblastoma	Assess the relationship between shunted hydrocephalus and intellectual, memory and academic functioning in a group of survivors of pediatric medulloblastoma	• As a group, these patients demonstrated low-average intellectual functioning with better-developed verbal than nonverbal abilities. • Low-average broad memory and VMI skills. • Reading scores in low end of the average range. Math and writing skills in the low-average range. • Those with VP shunts demonstrated significantly lower FSIQ scores and performance IQ scores than those without VP shunts. • Noted a trend for those with a VP shunt to score lower on the Perceptual Organization Index. • Patients with shunts had a lower processing speed index score (NS). • Patients with shunts exhibited significantly lower writing scores and lower math scores than non-shunted survivors. • Patients with shunts exhibited significantly greater impairments in visual-motor functioning. • The presence of hydrocephalus requiring the placement of a VP shunt was associated with more severe intellectual and academic deficits.
Hardy KK, Willard VW, Allen TM, et al. Working memory training in survivors of pediatric cancer: A randomized pilot study. Psychooncology 2013;22:1856-65.	2	11 survivors receiving adaptive treatment (intervention), 5 survivors receiving non-adaptive treatment (control)	To describe the feasibility and preliminary efficacy of an existing cognitive training program, *CogmedRM*, in a small, randomized clinical trial with survivors of pediatric brain tumors and ALL	• Majority of patients were fully compliant with the intervention. • Participants and their families reported high levels of satisfaction with training and no adverse events. • Adherent participants in the intervention arm exhibited significant improvement in visual working memory skills compared to those in the control arm, which persisted after 3 months without further training. • There were group differences in parent ratings of learning difficulties such that participants who completed the adaptive training were rated as having greater improvements in functioning immediately post-treatment. • Feasibility and preliminary efficacy of a home-based, computerized working memory training program, CogmedRM
Hardy KK, Willard VW, Bonner MJ. Computerized cognitive training in survivors of childhood cancer: a pilot study. J Pediatr Oncol Nurs. 2013;28:27-33	4a	9 children treated for CNS-affecting cancer	To pilot a computerized cognitive training program, *Captain's Log*, in a small sample of survivors of childhood cancer who demonstrated treatment-related attention and/or working memory difficulties	• Few technical problems reported (none prevented use/practice of program). No adverse events reported. • Wide range of time spent on intervention. • Working memory scores generally increased from baseline to follow-up assessments. • Parent-reported attention problems significantly decreased across time. • Changes in working memory modestly correlated with amount of time spent training and with response accuracy. Baseline IQ correlated positively with changes in Digit Span (Forward and Backward).

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Pediatr Blood Cancer DOI 10.1002/pbc

SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Hardy KK, Willard VW, Wigdor AB, et al. The potential utility of parent-reported attention screening in survivors of childhood cancer to identify those in need of comprehensive neuropsychological evaluation. Neurooncol Pract. 2015;2:32-39.	4a	70 survivors of pediatric cancer	Investigate the association between parent-rated attention problems and related neuropsychological impairments in childhood cancer survivors as a means of identifying those at high risk for difficulties	• 27% of survivors met symptom criteria for ADHD demonstrated greater impairments in IQ and working memory, but not processing speed, than survivors who did not. • ADHD symptom screening was associated with low sensitivity but stronger specificity for neuropsychological difficulties.
Harila MJ, Winqvist S, Lanning M, et al. Progressive neurocognitive impairment in young adult survivors of childhood acute lymphoblastic leukemia. Pediatr Blood Cancer. 2009;53:156-61.	4c	64 adult survivors of childhood ALL; 44 had cranial irradiation and 20 chemo-alone; 45 of survivors had earlier testing available for comparison; 45 healthy adult controls	To evaluate the neurocognitive performance of adult long-term survivors of childhood ALL and evaluate the impact of cranial irradiation on their cognitive functioning Test battery: verbal intelligence quotient (VIQ), performance intelligence quotient (PIQ), memory function, orientation and attention, and motor performance	• ALL survivors attained significantly lower test scores than the controls in all function areas. • Memory and motor functions were impaired among the irradiated survivor group compared with the controls. • A significant decline (repeated measures) in PIQ and VIQ test scores was observed in the irradiated survivor group during the follow-up period, but only in VIQ in the non-irradiated group.
Hile S, Erickson SJ, Agree B, et al. Parental stress predicts functional outcome in pediatric cancer survivors. Psychooncology. 2014;23:1157-64.	4a	N = 50 child-parent dyads. Children were ages 4-19 years who were at least 2 years post diagnosis with leukemia/lymphoma	Characterize frequency/severity of functional impairment and identify significant neurocognitive and psychosocial determinants of functional impairment	• 26% of the sample evidenced clinically significant functional impairment. • Regression analyses indicated that neurocognitive deficits did not predict functional impairment while parental stress was a significant predictor of functional impairment.
Hilverda K, Bosma I, Heimans JJ, et al. Cognitive functioning in glioblastoma patients during radiotherapy and temozolomide treatment: initial findings. J Neurooncol. 2010;97:89-94.	4a	13 newly diagnosed adult GBM patients	Prospectively examine cognitive functioning in newly-diagnosed, progression-free GBM patients at different points in time during combine radio-chemotherapy (measured before RT, after 6 weeks of RT/chemo, and after 3 cycles of adjuvant TMZ)	• Majority of patients had deficits in multiple cognitive domains at baseline. • In the course of the first 6 months of their disease, GBM patients treated with RT and TMZ, and who are not progressing, do not deteriorate in cognitive functioning.
Hiniker SM, Agarwal R, Modlin LA, et al. Survival and neurocognitive outcomes after cranial or craniospinal irradiation plus total-body irradiation before stem cell transplantation in pediatric leukemia patients with central nervous system involvement. Int J Radiat Oncol Biol Phys. 2014;89:67-74.	4a	41 pediatric ALL patients who had SCT with TBI plus additional craniospinal irradiation (CSI).	To evaluate survival and neurocognitive outcomes in pediatric ALL patients with CNS involvement, treated with a TBI containing SCT regimen and additional CSI	• Five year disease free survival was 67%. • Mean post-SCT IQ at 4.4 years post-SCT was 103.7. • Longitudinal analysis revealed no pre- to post-SCT change in IQ (although mean change was improvement of 4.7 points). • Relative deficiencies in processing speed and/or working memory in 38% of patients. • Overall the addition of CSI to the SCT regimen was well tolerated, with no evidence of significant cognitive impairment.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Hocking MC, Hobbie WL, Deatrick JA, et al. Neurocognitive and family functioning and quality of life among young adult survivors of childhood brain tumors. Clin Neuropsychol. 201;25:942-62.	7	NA	Reviews the types of neurocognitive late effects experienced by survivors of pediatric brain tumors	• Quantitative and qualitative data from three case reports of young adult survivors and their mothers are analyzed according to the theoretical model and presented in this paper to illustrate the importance of key factors presented in the model.
Hocking MC, Hobbie WL, Deatrick JA, et al. Family functioning mediates the association between neurocognitive functioning and health-related quality of life in young adult survivors of childhood brain tumors. J Adolesc Young Adult Oncol. 2015;4:18-25.	4a	34 Young adult-aged childhood BT survivors 18-30 years old	Examines the concurrent associations between survivor neurocognitive functioning, family functioning, and survivor emotional HRQOL, and the indirect effects of neurocognitive functioning on survivor emotional HRQOL through family functioning	• Poorer survivor processing speed, working memory, verbal memory, and executive function were significantly associated with worse survivor- and mother-reported family functioning. • Additionally, worse survivor processing speed and executive function were significantly associated with poorer survivor emotional HRQOL.
Hocking MC, McCurdy M, Turner E, et al. Social competence in pediatric brain tumor survivors: application of a model from social neuroscience and developmental psychology. Pediatr Blood Cancer. 2015;62:375-84.	7	NA	Discusses the current literature on survivor social functioning through a model of social competence in childhood brain disorder and suggests future directions based on this model	
Holland AA, Hughes CW, Harder L, et al. Effect of motivation on academic fluency performance in survivors of pediatric medulloblastoma. Child Neuropsychol. 2015;31:1-17.	4a	36 children who had completed treatment for medulloblastoma	Investigates the effect of enhanced extrinsic motivation on fluent (i.e., accurate and efficient) academic performance in pediatric medulloblastoma survivors	• Provision of a performance-based incentive resulted in statistically significant improvement, but not normalization of function, in performance on measures of academic fluency. • No demographic, treatment-related, academic, neuropsychological, or self-perception variables predicted response to incentive.
Horská A, Laclair A, Mohamed M, et al. Low cerebellar vermis volumes and impaired neuropsychologic performance in children treated for brain tumors and leukemia. AJNR Am J Neuroradiol. 2010;31:1430-7.	4b	10 patients treated with brain irradiation and 10 healthy controls	Evaluate early-delayed effects of radiAtion treatment on the cerebellar vermis in children with brain tumors or ALL to assess: changes in anterior and posterior vermal volumes and related neuropsychologic performance, the effect of radiation dose on changes in vermal volumes and neuropsychologic performance, and the association between vermal volumes and neuropsychologic performance following radiation	• There were lower relative volumes of anterior and posterior vermal subregions in patients diagnosed with brain malignancies and treated with combinations of surgery, chemotherapy and radiation. • Baseline Findings: • Lower vermal volumes were detected before radiation treatment was initiated or completed. • At baseline, impaired performance on tests of processing speed and motor speed was observed in patients • This remained unchanged 6 months postradiation. • Postradiation: • By 6 months postradiation, further decrease in vermal volumes was detected only in patients with medulloblastoma. • This was not associated with a corresponding decrease in processing-speed performance.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Howarth RA,Adamson AM, Ashford JM,et al. Investigating the relationship between COMT polymorphisms and working memory performance among childhoodbrain tumorsurvivors. Pediatr Blood Cancer. 2014;31:40-5.	4a	N = 50; mean age at irradiation 7.41±3.41; mean age at assessment 13.18±2.88	Examined the relationship between Catechol-O-methyltransferase(COMT) genotype and working memory performance among childhood brain tumor survivors	• Association between COMT genotype and performance on the self-ordered verbal (P = 0.03) but not object task (P = 0.33). • COMT may indicate a potential resiliency factor against neuro-cognitive effects of cancer and its treatment.
Howarth RA, Ashford JM, Merchant TE, et al. The utility of parent report in the assessment of working memory among childhood brain tumor survivors. J Int Neuropsychol Soc. 2013;19:380-9.	4b	50 brain tumor survivors that received irradiation and 40 siblings compared with 40 solid tumor survivors not receiving CNS-directed therapy	Study of the utility of parent report in detecting WM difficulties among childhood brain tumor survivors treated with conformal radiation therapy	• Parents rated brain tumor survivors as having significantly more WM problems ($p < .01$) compared to controls. • However, the BRIEF-WM scale demonstrated poor sensitivity and specificity for detecting performance-based problems. • Significant, albeit modest, correlations were found between the BRIEF-WM scale and performance measures ($r = -.24$ $-.22$; $p < .05$) for the combined group.
Ishida Y, Sakamoto N, Kamibeppu K, et al. Late effects and quality of life of childhood cancer survivors: Part 2. Impact of radiotherapy. Int J Hematol. 2010;92:95-104.	4b	113 childhood cancer survivors (CCS) treated with radiotherapy (RT) 72 CCS treated without RT 1000 matched controls	To investigate the late effects and QOL of CCS who were > 16 years old at time of study by comparing the outcomes of CCS treated with and without RT with a general population as a control Methods: Investigator grading of late effects through chart review Self-rating questionnaires on late effects and QOL	• Final heights were significantly lower in CCS with RT than in the other 2 groups. • Risk factors: TBI, spinal RT, age < 10 years at diagnosis. • Late effects observed in 68% of CCS with RT compared with 36% of CCS without RT. • Physical dysfunction, psychological stress, and problems of social adaptation observed in > 50% of CCS with RT. • TBI significantly associated with endocrine dysfunction. • Spinal irradiation significantly associated with short stature. • Skull and spinal irradiation were significantly associated with cognitive dysfunction (defined as >/= grade 2 AE on CTCAEv3).
Iuvone L, Mariotti P, Colosimo C, et al. Long-term cognitive outcome, brain computed tomography scan, and magnetic resonance imaging in children cured for acute lymphoblastic leukemia. Cancer. 2002;95:2562-70.	4a	21 children	Explore possible correlations between neuroimaging findings and neuropsychologic outcome in children treated for ALL with cranial irradiation (range, 18-24 Gy) plus intrathecal MTX	• White matter abnormalities were associated with poor performance only in a task exploring visual motor integration in 50% of patients. • Intracerebral calcifications correlate with the number of intrathecal MTX doses and with low scores in total intellectual quotient, performance intellectual quotient, and significant impairment in attention and visual motor integration tests. • Girls are more vulnerable to the effects of CNS prophylaxis, whereas age at treatment and radiotherapy dose are not relevant to neuropsychologic outcome.
Iuvone L, Peruzzi L, Colosimo C, et al. Pretreatment neuropsychological deficits in children with brain tumors. Neuro Oncol. 2011;13:517-24.	4a	83 children with newly diagnosed brain tumors	Cognitive status of children with brain tumors was examined prior to any treatment to single out the role of tumor and tumor-related factors in cognitive deficits	• Cognitive difficulties are detected at diagnosis in as many as 50% of patients for some cognitive domains; 6% of patients present with true-diagnosed mental retardation. • The location of the tumor is the principal determinant of cognitive deficits, with major impairment in children with cortical tumors.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Iyer NS, Balsamo LM, Bracken MB, et al. Chemotherapy-only treatment effects on long-term neurocognitive functioning in childhood ALL survivors: a review and meta-analysis. Blood. 2015 Jun 5. pii: blood-2015-02-627414.	1	10 non-experimental studies met all eligibility criteria	Meta-analysis assesses the long-term neurocognitive functioning after chemotherapy-only regimens among survivors of childhood ALL	• Significant moderate impairment across multiple neurocognitive domains evaluated, with intelligence most affected. • Working memory, information processing speed, and fine motor domains were moderately, but statistically significantly, impaired. Meta-analysis of ALL survivors treated without cranial radiation demonstrated significant impairment in IQ and other neuro-cognitive domains.
Jacola LM, Ashford JM, Reddick WE, et al. The relationship between working memory and cerebral white matter volume in survivors of childhood brain tumors treated with conformal radiation therapy.J Neurooncol. 2014;119:197-205.	4a	50 survivors (25 males, age at assessment 13.14 ± 2.88, age at CRT 7.41 ± 3.41 years)	Examined the association between white matter volume and working memory ability in survivors treated with conformal radiation therapy (CRT)	• Correlational analyses demonstrated that normal appearing white matter (NAWM) volumes were significantly larger in males and participants with tumors located in the infratentorial space. • Correlations between NAWM volume and Digit Span Backward were distributed across anterior and posterior regions, with evidence for greater right hemisphere involvement. Correlations between NAWM volume with Digit Span Backward and NAWM volume with SOS-Object Total were of greater magnitude in females. • No relationship was found between NAWM volume and caregiver report. • Working memory performance in survivors of pediatric BTs treated with CRT are related to regionally specific NAWM volume.
Jain N, Brouwers P, Okcu MF, et al. Sex-specific attention problems in long-term survivors of pediatric acute lymphoblastic leukemia. Cancer. 2009;115:4238-45.	4a	103 long-term survivors of ALL; 53 boys, 50 girls	To examine patterns of attention problems in survivors of pediatric ALL as a function of gender To determine if risk stratification of treatment mediated the attention problems	• Patients treated on high-risk protocols displayed significantly lower performance with sustained attention. However, children treated on high-risk protocols performed better on the measures of inhibitory control. • Girls performed worse than boys on measures related to the anterior attention system (shifting attention) and the subcortical attention system (sustained attention). • Boys performed worse than girls on different measures of anterior control (inhibition and working memory).
Jalali R, Mallick I, Dutta D, et al. Factors influencing neurocognitive outcomes in young patients with benign and low-grade brain tumors treated with stereotactic conformal radiotherapy. Int J Radiat Oncol Biol Phys. 2010;77:974-9.	4a	28 patients with residual or progressive brain tumors who were treated with stereotactic conformal RT; Median age 13yrs; Neuropsychological assessments before RT, 6 months after, & 24 months after RT	To evaluate the effect of radiotherapy doses to different volumes of normal structures of the brain on neurocognitive outcomes in young patients with benign and low-grade brain tumors treated prospectively with stereotactic conformal RT	• The overall mean FSIQ at baseline before RT did not change significantly at the 2 year follow-up evaluation. • 1/3 of patients showed a >10% decline in FSIQ as compared with baseline. • Patients with age < 15yrs at treatment had a significantly higher chance of developing a >10% drop in FSIQ. • Patients receiving > 43.2 Gy to > 13% of the volume of the left temporal lobe were at greater risk for a significant drop in FSIQ. • RT to the supratentorial brain, right temporal lobe and frontal lobes did not correlate with risk for drop in FSIQ.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Järvelä LS, Hurme S, Holopainen IE, et al. Auditory event related potentials as tools to reveal cognitive late effects in childhood cancer patients. Clin Neurophysiol. 2011;122:62-72.	3	27 newly diagnosed pediatric patients with leukemia or solid tumor (excluding CNS tumors) & 27 controls	To analyze ERP patterns (in particular, MMN and P3a patterns) in childhood cancer patients around the time of diagnosis and after treatment and to evaluate the clinical usefulness of this method in assessing potential treatment-related neurotoxicity	• MMN peak amplitude was attenuated in the patient group at diagnosis. • Between diagnosis and end of therapy, poorer enhancement of the MMN peak amplitude correlated with deterioration in the Verbal IQ in leukemia patients. • Prolongation of the MMN peak latency correlated with deterioration in the FSIQ and PIQ in the patient group. • Deterioration in the arithmetic subtest and PIQ correlated negatively with the age at diagnosis. • MMN changes between the studies associated with deterioration in the neuropsychological tests indicating that the method of evaluating ERP patterns could be clinically useful in screening for cognitive late effects.
Jayakar R, King TZ, Morris R, et al. Hippocampal volume and auditory attention on a verbal memory task with adult survivors of pediatric brain tumor. Neuropsychology. 2015;29:303-19.	4b	35 adult & 35 survivors	Examined the nature of verbal memory deficits and the possible hippocampal underpinnings in long-term adult survivors of childhood brain tumor	• Verbal memory indices of auditory attention list span and final list learning were significantly lower for survivors.
Kadan-Lottick NS, Brouwers P, Breiger D, et al. A comparison of neurocognitive functioning in children previously randomized to dexamethasone or prednisone in the treatment of childhood acute lymphoblastic leukemia. Blood. 2009;114:1746-52.	4b	92 ALL ≥1 yr off tx No CRT	To compare impact on neurocognitive function in patients treated with dexamethasone vs. prednisone during induction therapy	• Patients treated with Dex < Pred on reading ($p = 0.02$). • Both groups displayed increased rates of impairment on attention compared to norm. • Females treated with Pred < Dex on processing speed ($p = 0.03$). • Younger age had < IQ ($p = 0.02$), <process speed ($p = 0.02$), <spelling ($p = 0.02$) and <reading ($p = 0.01$) when treated with Pred vs. Dex.
			To examine influence of age at diagnosis and sex on neurocognitive outcomes	
Kadan-Lottick NS, Brouwers P, Breiger D, et al. Comparison of neurocognitive functioning in children previously randomly assigned to intrathecal methotrexate compared with triple intrathecal therapy for the treatment of childhood acute lymphoblastic leukemia. J Clin Oncol. 2009; 27:5986-92.	4b	171ALL ≥1 yr off tx No CRT	To compare impact on neurocognitive function in patients treated with IT MTX vs. TIT	• Patients treated with IT MTX < TIT on processing speed. • IT MTX group increased rate of impairment on visual-motor compared to norm. • Both groups increased rate of impairment on attention compared to norm. • Both groups better than norm on reading.
			To examine influence of age at diagnosis and sex on neurocognitive outcomes	

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Kadan-Lottick NS, Zeltzer LK, Liu Q, et al. Neurocognitive functioning in adult survivors of childhood non-central nervous system cancers. J Natl Cancer Inst. 2010;102:881-93.	4a	5937 non-CNS >5 yrs off tx 382 siblings	To describe neurocognitive function in survivors of non-CNS cancers of childhood. To compare function to sibling cohort To identify treatment and patient predictors of function	• Survivors < siblings on task efficiency, memory, emotional regulation. • ALL, AML, and NHL most impaired. • Age < 6 yrs, female sex, CRT, and hearing impairment increased risk for impairment.
Kahalley LS, Conklin HM, Tyc VL, et al. Slower processing speed after treatment for pediatric brain tumor and acute lymphoblastic leukemia. Psychooncology. 2013;22:1979-86.	4b	50 ALL & 50 BT (ages 12-17 yrs)	To estimate discrepancies between processing speed and estimated IQ	• General reasoning abilities remains intact, however, BT and ALL survivors exhibit slower processing speed. Global measures of intellectual ability will underestimate dysfunction in survivors.
Kamdar KY, Krull KR, El-Zein RA, et al. Folate pathway polymorphisms predict deficits in attention and processing speed after childhood leukemia therapy. Pediatr Blood Cancer. 2011;57:454-60.	4a	72 childhood ALL survivors	Evaluated the relationship between folate pathway polymorphisms and neurocognitive impairment after childhood ALL chemotherapy	• General neurocognitive impairment on the neurocognitive battery was related to 10-methylenetetrahydrofolate reductase 1298A>C and methionine synthase 2756A>G ($P = 0.05$).
Kenzik KM, Huang IC, Brinkman TM, et al. The Childhood Cancer Survivor Study-Neurocognitive Questionnaire (CCSS-NCQ) revised: item response analysis and concurrent validity. Neuropsychology. 2015;29:31-44.	4a	833 adult survivors of childhood cancer	Validated the Childhood Cancer Survivor Study-Neurocognitive Questionnaire	• Items captured low to middle levels of neurocognitive concerns. • The latent domain scores demonstrated poor convergent/divergent validity with the direct assessments. • Adjusted effect sizes for agreement between self-reported memory and direct memory assessment were moderate for total recall, long-term memory, and short-term memory.
Kesler SR, Tanaka H, Koovakkattu D. Cognitive reserve and brain volumes in pediatric acute lymphoblastic leukemia. Brain Imaging Behav. 2010;4:256-69.	4b	28 ALL ≥ 6 mo post tx (non-CRT) 1 of 8 protocols 31 healthy controls	To examine WM volume and cognition in ALL vs. healthy controls To examine cognitive reserve (maternal education, brain volume, cognitive outcome)	• ALL group lower WM volume (frontal), but not total brain volume. • Effects mediated by maternal education.
Kesler SR, Lacayo NJ, Jo B. A pilot study of an online cognitive rehabilitation program for executive function skills in children with cancer-related brain injury. Brain Injury. 2011;25; 101-12.	3	23 (14 ALL, 9 CNS tumors) ≥ 6 mo post tx 7-19 yrs old	To examine efficacy of cognitive rehabilitation of executive function	• 8-14 week, 40 session web intervention associated with improved processing speed, memory, and cognitive flexibility. • Intervention associated with increased fMRI activity in frontal cortex.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Khajuria RK, Blankenburg F, Wuithschick I, et al. Morphological brain lesions of pediatric cerebellar tumor survivors correlate with inferior neurocognitive function but do not affect health-related quality of life. Childs Nerv Syst. 2015;31:569-80.	4b	17 cerebellar pilocytic astrocytoma (cPA) and 17 medulloblastoma (MB) survivors were examined	Determine whether extent of morphological brain injury in pediatric cerebellar tumor survivors correlates with neurocognitive function and health-related quality of life	• Significant correlations between amount and extent morphological brain lesions of pediatric cerebellar tumor survivors and several cognitive impairments including intelligence and attention in both patient groups.
Khong PL, Leung LH, Fung AS, et al. White matter anisotropy in post-treatment childhood cancer survivors: preliminary evidence of association with neurocognitive function. J Clin Oncol. 2006;24:884-90.	4b	30 MED and ALL survivors	Determine if the loss of white matter fractional anisotropy (FA), measured by diffusion tensor magnetic resonance imaging (DTI), in post-treatment childhood medulloblastoma (MED) and acute lymphoblastic leukemia (ALL) survivors correlate with intelligence quotient (IQ) scores	• Delta FA% had a significant effect on FSIQ (adjusted $r2 = 0.439$; $P < .001$), VIQ (adjusted $r(2) = 0.237$; $P = .028$), and PIQ (adjusted $r(2) = 0.491$; $P < .001$) after adjusting for the effects of age at treatment, irradiation dose, and time interval from treatment.
Kirchhoff AC, Krull KR, Ness KK, et al. Physical, mental, and neurocognitive status and employment outcomes in the childhood cancer survivor study cohort. Cancer Epidemiol Biomarkers Prev. 2011;20:1838-49.	4b	5,386 unemployed and 3,763 employed CCSS adults	Examined the relationship of physical, mental, and neurocognitive function with employment and occupational status in the Childhood Cancer Survivor Study (CCSS)	• Male survivors with somatization and memory problems were approximately 50% more likely to report this outcome, whereas task efficiency limitations were significant for both sexes.
Knight SJ, Conklin HM, Palmer SL, et al. Working memory abilities among children treated for medulloblastoma: parent report and child performance. J Pediatr Psychol. 2014;39:501-11.	4a	167 children with meduloblastoma	To investigate the 5-year postsurgical developmental trajectory of working memory (WM) in children with medulloblastoma using parent and performance-based measures	• Most children treated for medulloblastoma display WM within the age-appropriate range according to parent report and performance. • However, the subtle negative changes over time and identified subgroups at increased risk highlight the need for ongoing monitoring of this population.
Kramer JH, Crittenden MR, DeSantes K, et al. Cognitive and adaptive behavior 1 and 3 years following bone marrow transplantation. Bone Marrow Transplant. 1997;19; 607-13.	4a	Children < 18 years, but predominantly young (< 6 years); 67 assessed 1 yr post-SCT, and 26 assessed 3 yrs post SCT (from cohort of 137 pre-SCT)	Examined change in developmental and cognitive functioning in a prospective, longitudinal design	• Significant decline at 1-yr post SCT • No relationship of 1-yr post SCT functioning with diagnosis, type of SCT, use of TBI, age or gender • Deficits maintained at 3-yrs post SCT, but no further declines • Very young sample, with mean age of 45 months; restricted age range limits ability to detect age effects

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Krappmann P, Paulides M, Stöhr W, et al. Almost normal cognitive function in patients during therapy for childhood acute lymphoblastic leukemia without cranial irradiation according to ALL-BFM 95 and COALL 06-97 protocols: results of an Austrian-German multicenter longitudinal study and implications for follow-up. Pediatr Hematol Oncol. 2007;24:101-9.	4a	66 childhood ALL patients	Prospectively investigated neurocognitive function in childhood ALL patients	• There was a statistically significant decline of intellectual function after reinduction therapy for younger patients and girls (IQ scores still within normative data range), there were no differences in visual-motor performance and concentration over the time of induction therapy.
Krawczuk-Rybak M, Grabowska A, Protas PT, et al. Intellectual functioning of childhood leukemia survivors--relation to Tau protein--a marker of white matter injury. Adv Med Sci. 2012;57:266-72.	4a	31 survivors of childhood ALL (6.3 years after diagnosis)	Analysed the cognitive functions of ALL survivors in relation to Tau protein	• ALL survivors attained the average scores in intelligence tests. • A negative correlation was found between methotrexate (MTX) doses and Freedom from Distractibility (FFD). Females had higher values of Performance Intelligence Quotient (PIQ) than males. • A negative correlation was noted of Tau protein levels obtained from the last CSF with: Total and Verbal Intelligence Quotient, PIQ, Perceptual Organisation Index and FFD but not with Verbal Comprehension Index.
Krull KR, Annett RD, Pan Z, et al. Neurocognitive functioning and health-related behaviours in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Eur J Cancer. 2011;47:1380-8.	4a	6,440 adult survivors from the Childhood Cancer Survivor Study	Neurocognitive function and emotional distress were examined in adult survivors from the Childhood Cancer Survivor Study	• Survivors with neurocognitive problems in task efficiency were less likely to meet the Centers for Disease Control guidelines for weekly physical activity. • Survivors with neurocognitive impairment were more likely to engage in general survivor care and less likely to engage in dental care.
Krull KR, Bhojwani D, Conklin HM, et al. Genetic mediators of neurocognitive outcomes in survivors of childhood acute lymphoblastic leukemia.J Clin Oncol. 2013;31:2182-8.	4a	243 survivors treated on an institutional protocol featuring risk-adapted chemotherapy without prophylactic cranial irradiation	Examined genetic polymorphisms associated with variability in neurocognitive outcome among children treated for ALL	• Compared with national norms, the cohort demonstrated significantly higher rates of problems on direct assessment of sustained attention and on parent ratings of attention problems. • Children with the A2756G polymorphism in methionine synthase (MS) were more likely to demonstrate deficits in attentiveness and response speed, whereas those with various polymorphisms in glutathione S-transferase demonstrated increased performance variability and reduced attentiveness. Polymorphisms in monoamine oxidase (T1460CA) were associated with increased attention variability. • Parent-reported attention problems were more common in children with the Cys112Arg polymorphism in apoliopoprotein E4.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Krull KR, Brinkman TM, Li C, et al. Neurocognitive outcomes decades after treatment for childhood acute lymphoblastic leukemia: a report from the St Jude lifetime cohort study. J Clin Oncol. 2013;31:4407-15.	4a	1,014 survivors (age GE 18 years) were eligible, 738 (72.8%) agreed to participate, and 567 (76.8%) of these were evaluated	To determine rates, patterns, and predictors of neurocognitive impairment in adults decades after treatment for childhood acute lymphoblastic leukemia (ALL)	• Impairment rates across neurocognitive domains ranged from 28.6% to 58.9%, and those treated with chemotherapy only demonstrated increased impairment in all domains. • In survivors who received no CRT, dexamethasone was associated with impaired attention and executive function. • The impact of CRT was dependent on young age at diagnosis for intelligence, academic, and memory functions. • Risk for executive function problems increased with survival time in a CRT dose-dependent fashion. In all survivors, self-reported behavior problems increased by 5% with each year from diagnosis. Impairment was associated with reduced educational attainment and unemployment.
Krull KR, Hockenberry MJ, Miketova P, et al. Chemotherapy-related changes in central nervous system phospholipids and neurocognitive function in childhood acute lymphoblastic leukemia. Leuk Lymphoma. 2013;54:535-40.	4a	76 children undergoing chemotherapy for acute lymphoblastic leukemia	Explores associations between changes in cerebrospinal fluid (CSF) phospholipids and neurocognitive function in children undergoing chemotherapy for acute lymphoblastic leukemia	• Associations between post-induction SM and motor speed at 1 year, 2 years and 3 years following diagnosis. • Post-induction lysophosphatidylcholine was associated with verbal working memory.
Krull KR, Khan RB, Ness KK, et al. Symptoms of attention-deficit/hyperactivity disorder in long-term survivors of childhood leukemia. Pediatr Blood Cancer. 2011;57:1191-6.	4a	161 ALL $\geq$ 5 yrs post tx	To estimate occurrence of ADHD symptoms in survivors To examine clinical correlates To compare to indices of brain integrity	• 10.5% met full DSM-IVR criteria for ADHD. • Distractibility and forgetfulness most common. • 36.6% reported pervasive symptoms; 25.5% reported symptoms impair function. • CRT and neurologic soft-signs associated with inattention; no patient or treatment characteristics associated with hyper/impulsive symptoms.
Krull KR, Minoshima S, Edelmann M, et al. Regional brain glucose metabolism and neurocognitive function in adult survivors of childhood cancer treated with cranial radiation. J Nucl Med. 2014;55:1805-10.	4a	38 adult survivors of ALL	Examine associations between regional brain metabolism, as measured by PET, and neurocognitive outcomes in adult survivors of childhood ALL	• Compared with national norms, survivors demonstrated lower vocabulary ($P < 0.001$), reading ($P < 0.001$), mathematics ($P < 0.001$), working memory ($P < 0.001$), oral naming speed ($P < 0.001$), and cognitive flexibility ($P < 0.001$). • Metabolic activity was higher in basal gangliar structures for those treated with 24 Gy of cranial radiation therapy ($P = 0.04$). • Metabolic activity was positively correlated with oral naming speed in both lateral frontal lobes ($\rho = 0.48$ and 0.47 for right and left frontal regions, respectively, $P < 0.01$) and negatively correlated with cognitive flexibility in the sections of the basal ganglia ($P < 0.01$ for both caudate and putamen).
Krull KR, Okcu MF, Potter B, et al. Screening for neurocognitive impairment in pediatric cancer long-term survivors. J Clin Oncol. 2008;26:4138-43.	4a	240 consecutive patients in a long-term survivor clinic	Reports reliability and validity data on a brief neurocognitive screening method that could be used to routinely screen patients in need of comprehensive follow-up	• The screen accurately predicted global intellect ($F(6,45) = 11.81$, $P < .0001$), reading skills ($F(6,45) = 4.74$, $P < .001$), and mathematics ($F(6,45) = 3.35$, $P < .008$).

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Krull KR, Sabin ND, Reddick WE, et al. Neurocognitive function and CNS integrity in adult survivors of childhood hodgkin lymphoma. J Clin Oncol. 2012;30:3618-24.	4a	62 adult survivors	Aim of this study was to examine neurocognitive and brain imaging outcomes in adult survivors of childhood Hodgkin lymphoma(HL)	• HL survivors demonstrated lower performance on sustained attention (P = .004), short-term memory (P = .001), long-term memory (P = .006), working memory (P < .001), naming speed (P < .001), and cognitive fluency (P = .007). • MRI revealed leukoencephalopathy in 53% of survivors, and 37% had evidence of cerebrovascular injury.
Kunin-Batson A, Kadan-Lottick N, Neglia JP. The contribution of neurocognitive functioning to quality of life after childhood acute lymphoblastic leukemia. Psychooncology. 2014;23:692-9.	4a	263 ALL survivors (ages 7-17 years) treated on similar legacy COG chemotherapy protocols without radiation	To examine the relative influence of neurocognitive functioning, steroid randomization (prednisone vs. dexamethasone), and demographic characteristics on QOL in first-remission survivors of childhood ALL	• Children and their parents reported lower mean child psychosocial QOL than healthy population norms ($p < 0.05$), but were not in the impaired range. • Physical QOL was similar to population norms. • Though neurocognitive difficulties were predominantly mild for the sample as a whole, neurocognitive deficits, specifically problems in verbal cognitive abilities and visual-motor integration skills, were significantly associated with poor physical ($p < 0.01$) and Psychosocial QOL ($p < 0.01$). QOL was not associated with previous steroid randomization.
Kunin-Batson A, Kadan-Lottick N, Zhu L, et al. Predictors of independent living status in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Pediatr Blood Cancer. 201;57:1197-203.	4b	Adult survivors of childhood cancers (n = 6,047) and siblings (n = 2,326), all 25 years of age and older	Assess adaptive, neurocognitive, and psychological functioning, as well as demographic and health status	• Compared to siblings, survivors were more than twice as likely to live dependently. • Survivors diagnosed with CNS tumors or leukemia were significantly less likely to live independently compared to those diagnosed with Hodgkin lymphoma. • Other risk factors for reduced independent living included cranial radiation, use of neuroleptic, anticonvulsant, or psychostimulant medication, attention and processing speed problems, poor physical functioning, depression, and racial/ethnic minority status.
Küpeli S, Yalçın B, Bilginer B, et al. Posterior fossa syndrome after posterior fossa surgery in children with brain tumors. Pediatr Blood Cancer. 2011;56:206-10.	4a	36 posterior fossa tumor	To determine incidence of posterior fossa syndrome To define the risk factors for PFS and determine accompanying neurobehavior problems	• Pre- vs. post-op testing revealed PFS in 9 (25%) patients. • Medulloblastoma, midline tumors, and low SES were significant risk factors. • No IQ differences between groups with and without PFS.
Kupst MJ, Penati B, Debban B, et al. Cognitive and psychosocial functioning of pediatric hematopoietic stem cell transplant patients: A prospective longitudinal study. Bone Marrow Transplant. 2002;30:609-617.	4a	Children 0-18 years assessed pre-SCT, and at 1-yr (n = 153) and 2-yrs (n = 70) post SCT (from cohort of 377 assessed pre-SCT)	Examine changes in cognitive and psychoeducational function in SCT survivors using a prospective, longitudinal design	• No significant changes in pre-post comparisons. • Mean global scores in the average range. • No evidence of decline in youngest (< 3 years) patient group. • Primary predictor of cognitive outcome was pre-SCT function. • SCT survivors demonstrated a low prevalence of social and behavioral problems.

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Pediatr Blood Cancer DOI 10.1002/pbc

SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Laffond C, Dellatolas G, Alapetite C, et al. Quality-of-life, mood and executive functioning after childhood craniopharyngioma treated with surgery and proton beam therapy. Brain Inj. 2012;26:270-81.	4a	23 children with craniopharyngioma	Examine association with neurocognitive and psychological morbidity, and quality-of-life	• QoL self-report was within the normal range. • QoL proxy-report was lower than self-report. • Eleven patients reported depression. • 24-38% had dysexecutive symptoms. • Depression and low parental educational level were associated with lower QoL and higher levels of executive dysfunction.
Lai JS, Zelko F, Krull KR, et al. Parent-reported cognition of children with cancer and its potential clinical usefulness. Qual Life Res. 2014;23:1049-58.	4a	515 children with cancer at all stages of disease	Assess clinical utility of parent report of child's perceived cognitive function and CogState	• Perceived cognitive function distinguished between children with and without brain tumors and time since diagnosis. • Perceived cognitive function correlated with CogState on 40 or 60 comparisons.
Langer T, Martus P, Ottensmeier H, et al. CNS late-effects after ALL therapy in childhood. Part III: neuropsychological performance in long-term survivors of childhood ALL: impairments of concentration, attention, and memory. Med Pediatr Oncol. 2002;38:320-8.	4a	38 non-cranially irradiated MTX-group and 83 cranially irradiated RT-group	Purpose was to define the neuropsychological function and to describe which central nervous system (CNS) functions are impaired following the German ALL-BFM and COALL protocols for CNS-negative patients	• RT-group exhibited a lower Full Scale IQ than the MTX-group. • Particularly for the Kaufman factor Freedom from Distractibility the RT-group showed the lower scores. • Significant interactions between gender and CNS prophylactic treatment were observed for Full Scale IQ, Verbal IQ, Performance IQ, Verbal Comprehension, and Perceptual Organization.
Larysz D, Blamek S, Larysz P, et al. Posterior fossa brain tissue injury: developmental, neuropsychological, and neurological consequences of brain tumors in children. Acta Neurochir Suppl. 2010;106:271-4.	4b	34 children (14 cerebellar, 20 non-cerebellar) 5-21 yrs old	To assess neurodevelopment in posterior fossa tumors. To examine clinical correlates of neurocognitive function	• CRT associated with worse WISC PRI. • Worse outcome for tumors in cerebellum. • Working memory better in "older" children.
Law N, Bouffet E, Laughlin S, et al. Cerebello–thalamo–cerebral connections in pediatric brain tumor patients: Impact on working memory. Neuroimage. 2011;56:2238-48.	4b	29 children with cranial radiation; 12 surgery only; 26 health controls	Investigated how brain injury following treatment for posterior fossa tumors results in deficits in working memory	• Poorer working memory scores were observed for the cranial radiation group relative to controls. • Reduced anisotropy and higher radial diffusivity within the entire cerebello–thalamo–cerebral pathway predicted lower working memory.
Leung W, Hudson MM, Strickland DK, et al. Late effects of treatment in survivors of childhood acute myeloid leukemia. J Clin Oncol. 2000;18:3273-9.	4a	77 survivors	Investigate the incidence of and risk factors for late sequelae of treatment in patients who survived for more than 10 years after the diagnosis of childhood acute myeloid leukemia (AML)	• Growth abnormalities were found in 51% of survivors, neurocognitive abnormalities in 30%, transfusion-acquired hepatitis in 28%, endocrine abnormalities in 16%, cataracts in 12%, and cardiac abnormalities in 8%.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Luxton J, Brinkman TM, Kimberg C, et al. Utility of the N-back task in survivors of childhood acute lymphoblastic leukemia. J Clin Exp Neuropsychol. 2014;36:944-55.	4a	137 survivors of acute lymphoblastic leukemia (ALL	Examines functional brain imaging studies and working memory networks	• Females demonstrated significantly slower reaction times than males. • Survivors <15 years old at the time of testing demonstrated a significant decrease in accuracy as working memory load increased compared to survivors ≥15 years old. • Performance on the N-back task was associated with nonverbal working memory in survivors ≥15 years of age. • For younger survivors, N-back performance was more strongly associated with attention skills.
Mabbott DJ, Monsalves E, Spiegler BJ, et al. Longitudinal evaluation of neurocognitive function after treatment for central nervous system germ cell tumors in childhood. Cancer 2011;117:5402–11.	4a	35 children (M age 11 years) seen after diagnosis and treatment for a CNS GCT	Longitudinal neurocognitive outcome in CNS GCT patients seen for neuropsychological evaluation at a single institution was examined	• Intelligence, academic functioning, and receptive vocabulary were not significantly compromised in most patients treated for CNS GCT. • Working memory, information processing speed, and visual memory declined significantly over time in all patients. Patients with pineal tumors showed early and stable deficits, whereas patients with suprasellar and bifocal tumors showed more protracted declines from initial average functioning. • Children treated with ventricular versus craniospinal radiation displayed better outcome.
Mabbott DJ, Noseworthy MD, Bouffet E, et al. Diffusion tensor imaging of white matter after cranial radiation in children for medulloblastoma: correlation with IQ. Neuro Oncol. 2006;8:244-52.	4b	8 patients and 8 control children	Examined apparent diffusion coefficient (ADC), fractional anisotropy (FA), and intelligence in pediatric patients treated with CSR for medulloblastoma relative to control subjects	• Decreased IQ was associated with increased ADC and decreased FA. Mean IQ for the CSR group was lower than that for the control group, but the difference was not significant when controlling for overall mean FA or ADC.
Mabbott DJ, Penkman L, Witol A, et al. Core neurocognitive functions in children treated for posterior fossa tumors. Neuropsychology. 2008;22:159-68.	4a	64 patients	Evaluated sustained attention, information processing speed, working memory, and IQ in children with with posterior fossa tumors	• Neither age at, nor time since, diagnosis predicted cognitive outcome in this sample. • Further, sustained attention and working memory were largely intact and there were no differences between groups. • Patients treated with cranial radiation demonstrated lowered short-form IQ and slow information processing speed: Patients treated with cranial radiation and who experienced postsurgical complications demonstrated the poorest performance.
Mabbott DJ, Snyder JJ, Penkman L, et al. The effects of treatment for posterior fossa brain tumors on selective attention. J Int Neuropsychol Soc. 2009;15:205-216.	4b	54 patients with either (1) posterior fossa (PF) tumors treated with cranial radiation and surgery ($n = 22$); (2) PF tumors treated with surgery alone ($n = 17$); or (3) non-CNS tumors ($n = 15$)	Identify whether deficits in selective attention are present in pediatric brain tumor patients	• PF tumor patients selective attention was impaired, regardless of whether they were treated with cranial radiation and surgery or surgery alone. • Patients treated with cranial radiation were most impaired.

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Pediatr Blood Cancer DOI 10.1002/pbc

SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
MaddreyAM, Bergeron JA, Lombardo ER, et al. Neuropsychological performance and quality of life of 10 year survivors of childhood medulloblastoma. J Neurooncol. 2005:72:245-53.	4a	16 medulloblastoma survivors were tested at a mean age of 22.2 years	Cognitive performance, psychosocial functioning and quality of life were assessed in medulloblastoma survivors in the second decade after diagnosis	• Significant impairments were identified in survivors on tests within all neuropsychological domains. • Significant impairments were also identified in all psychosocial domains examined, including employment, ability to drive an automobile, participation in normal education, independent living, and dating history. • Quality of life scores, reported by both survivors and their caretakers, were in the normal range.
Mahone EM, Prahme MC, Rugle K, et al. Motor and perceptual timing deficits among survivors of childhood leukemia. J Pediatr Psychol. 2007;32:918-25.	4b	N = 22 ALL and 22 controls	Examine cerebellar-frontal system change in children treated for leukemia with chemotherapy	• After controlling for IQ, the ALL group had poorer performance than controls on judgment of long duration and motor timing, but not judgment of pitch.
Merchant TE, Conklin HM, Wu S, et al. Late effects of conformal radiation therapy for pediatric patients with low-grade glioma: prospective evaluation of cognitive, endocrine, and hearing deficits. J Clin Oncol. 2009;27:3691-7.	4b	78 LGG (58 diencephalon, 3 cerebrum, 17 cerebellum)	To estimate incidence, time to onset, and severity of CNS dysfunction in LGG	• From baseline to 5 yr follow-up, improvement in internalizing problems and working memory, decline in reading, spelling, communication. • NF associated with lower baseline IQ, reading, spelling, communication. • Hx hydrocephalus associated with lower memory. • CRT at younger age worse than older age.
Merchant TE, Sharma S, Xiong X, et al. Effect of cerebellum radiation dosimetry on cognitive outcomes in children with infratentorial ependymoma.Int J Radiat Oncol Biol Phys. 2014;90:547-53.	4a	76 children (39 males) at a median 3.3 years of age (range, 1-17 years old) were irradiated for infratentorial ependymoma	Examine the effect of RT on cerebellum-linked neurocognitive deficits. Age-appropriate cognitive and academic testing was performed prior to the start of RT and was then repeated at 6 months and annually throughout 5 years	• A correlation between mean infratentorial dose and intelligence quotient, math, reading, and spelling scores, where Gy was measured as the difference between the mean dose received by an individual patient and the mean dose received by the patient group. • There was a correlation between mean anterior cerebellum dose and IQ scores and mean posterior cerebellum dose and IQ, math, reading, and spelling scores.
Mohrmann C, Henry J, Hauff M, et al. Neurocognitive outcomes and school performance in solid tumor cancer survivors lacking therapy to the central nervous system. J Pers Med. 2015;5:83-90.	4a	58 pediatric extra-cranial solid tumor patients	Examined medical records of young pediatric extracranial solid tumor patients who lacked CNS-directed therapy or other known risk factors for cognitive impairment to evaluate the incidence of reported difficulties or abnormalities in neuropsychological testing	• 31% of patients were found to have at least one reported difficulty or abnormality. Of note, 34% of patients with Wilms tumor possessed difficulties compared to 23% of patients with other extracranial solid tumors. • Extracranial solid tumor cancer survivors without known risk factors for school performance difficulties appear to have a higher incidence of problems than expected.
Montour-Proulx I, Kuehn SM, Keene DL, et al. Cognitive changes in children treated for acute lymphoblastic leukemia with chemotherapy only according to the Pediatric Oncology Group 9605 protocol. J Child Neurol. 2005;20:129-33.	4a	26 children; Mean age at diagnosis 4.88 +/- 2.54 years	Examine cognitive functioning and neuroimaging in children with leukemia treated with the Pediatric Oncology Group 9605	• The proportion of scores on measures of intelligence and memory falling > 1 SD below the normative mean was substantially higher than expected. Paired t-test suggested that Wechsler Verbal IQ and memory remained stable, whereas Wechsler Performance IQ declined significantly. • 78% of the group showed leukoencephalopathy on at least one magnetic resonance image. • Reliance on seizures as a predictor of leukoencephalopathy might underestimate the incidence of neurotoxicity.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Moore BD 3rd. Neurocognitive outcomes in survivors of childhood cancer. J Pediatr Psychol. 2005;30:51-63.	7	NA	Reviews issues associated with neurocognitive outcome in survivors of pediatric cancer	
Moore IM, Hockenberry MJ, Anhalt C, et al. Mathematics intervention for prevention of neurocognitive deficits in childhood leukemia. Pediatr Blood Cancer. 2012;59:278-84.	2	15 survivors receiving intervention, 17 survivors receiving standard care	To determine if the mathematics intervention was effective in preventing declines in mathematics ability among children newly diagnosed with ALL	• Improved applied mathematics at T2 and T3. Improvement in calculation skills at T2, returned to baseline by T3. Improvement in visual working memory at T2 and T3. No differences seen in mathematics for control group. (*T1 = baseline; T2 = end of intervention; T3 = 1 year post-intervention).
Moxon-Emre I, Bouffet E, Taylor MD, et al. Impact of craniospinal dose, boost volume, and neurologic complications on intellectual outcome in patients with medulloblastoma. J Clin Oncol. 2014;32:1760-8.	4a	113 patients treated for medulloblastoma	Examine the impact of radiation (ie, craniospinal irradiation [CSR] dose and boost volume) and complications (i.e., hydrocephalus and other neurologic complications, including mutism) on patterns of change in intellectual functioning in medulloblastoma survivors.	• Patients treated with reduced-dose CSR plus TB boost showed stable intellectual trajectories, whereas patients treated with higher doses and larger boost volumes experienced intellectual declines.
Mulhern RK, Khan RB, Kaplan S, et al. Short-term efficacy of methylphenidate: a randomized, double-blind, placebo-controlled trial among survivors of childhood cancer. J Clin Oncol. 2004;22:4795-803.	2	83 long-term survivors of ALL and BT with attentional deficits	To test the hypothesis that the psychostimulant methylphenidate (MPH) improves cognitive and social functioning in this group	• Compared to placebo, significant improvement with MPH was reported by teachers and parents on the Conners' Rating Scales and by teachers on the Social Skills Rating System. • However, no consistent advantage of moderate dose over low dose was observed. Of those participating, 66 (79.5%) of the 83 patients continued on best clinical management.
Mulhern RK, Merchant TE, Gajjar A, et al. Late neurocognitive sequelae in survivors of brain tumours in childhood. Lancet Oncol. 2004;5:399-408.	7	N/A	To describe the late neurocognitive sequelae in survivors of posterior fossa brain tumors (>2 years after completion of treatment), the risk factors for these sequelae, their pathophysiology, and ways to limit their occurrence	• Less severe deficits if post-operative radiation confined to posterior fossa alone (e.g. ependymoma) or surgery alone (e.g. low grade astrocytoma) vs craniospinal radiation. • Younger age, higher radiotherapy dose and time from treatment are risk factors for sequelae. • Hydrocephalus, posterior fossa syndrome may be risk factors. • Cerebral white matter loss post radiation related to performance on tests of IQ, attention and academic achievement. • Amelioration or treatment of cognitive deficits may be addressed by: innovations in radiotherapy, cognitive remediation, pharmaco-therapy (i.e. methylphenidate), environmental interventions.
Mulhern RK, Palmer SL. Neurocognitive late effects in pediatric cancer. Curr Probl Cancer, 2003;27:177–197.	7	NA	Provides an interpretation of research findings within a conceptual framework that can be used to accommodate new studies as well as to guide future research	
Mulhern RK, Palmer SL, Merchant TE, et al. Neurocognitive consequences of risk-adapted therapy for childhood medulloblastoma. J Clin Oncol. 2005;23:5511-19.	4a	111 children with medulloblastoma	To examine long-term effects of risk adapted craniospinal irradiation on intelligence and academic achievement in children treated for medulloblastoma	• Significant declines in IQ (-1.59 points/yr), reading (-2.95 points/yr), spelling (-2.94 points/yr), and math (-1.87 points/yr) were observed for the entire group. • Greater declines were associated with younger age at diagnosis particularly in the high risk group.

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Pediatr Blood Cancer DOI 10.1002/pbc

SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Mulhern RK, Palmer SL, Reddick WE, et al. Risks of young age for selected neurocognitive deficits in medulloblastoma are associated with white matter loss. J Clin Oncol. 2001;19:472-9.	4a	42 children with medulloblastoma	To test the hypothesis that inadequate development of normal-appearing white matter (NAWM) is associated with the relationship between young age at the time of craniospinal irradiation (CRT) and deficient neurocognitive performance in survivors of childhood medulloblastoma	• NAWM accounted for a significant amount of the association between age at CRT and IQ, factual knowledge, and verbal and nonverbal thinking, but not sustained attention or verbal memory.
Mulhern RK, Reddick WE, Palmer SL, et al. Neurocognitive deficits in medulloblastoma survivors and white matter loss. Ann Neurol. 1999;46:834-41.	4b	18 pediatric patients previously treated for MED were matched on the basis of age at the time of evaluation to 18 patients previously treated for low-grade posterior fossa tumors with surgery alone	Test the hypotheses that (1) patients treated for MED in childhood have reduced volumes of normal white matter (NWM) related to their treatment with craniospinal irradiation with or without chemotherapy, and (2) deficits in NWM among patients surviving MED can at least partially explain deficits in their intellectual performance	• Children treated for MED had significantly less NWM and significantly lower Full-Scale IQ values than those treated for low-grade tumors. • NWM had a positive and statistically significant association with Full-Scale IQ among the patients treated for MED.
Mulhern RK, White HA, Glass JO, et al. Attentional functioning and white matter integrity among survivors of malignant brain tumors of childhood. J Int Neuropsychol Soc. 2004;10:180-9.	4a	37 long-term survivors of malignant brain tumors	Exmines effects of treatment on normal appearing white matter (NAWM) on MRI and the influence of NAWM volumes on neurocognitive functioning	• On the Conners' Continuous Performance Test, the Overall Index and 7 of the other 10 indices were significantly deficient compared to age- and gender-corrected normative values. • After statistically controlling for the effects of age at diagnosis and time elapsed from treatment, 5 of the 8 indices were significantly associated with cerebral white matter volumes and/or specific regional white matter volumes of the prefrontal/frontal lobe and cingulate gyrus.
Nathan PC, Patel SK, Dilley K, et al. Guidelines for identification of, advocacy for, and intervention in neurocognitive problems in survivors of childhood cancer: a report from the Children's Oncology Group. Arch Pediatr Adolesc Med. 2007;161:798-806.	7	NA	Follow-up Guidelines Task Force on Neurocognitive/Behavioral Complications After Childhood Cancer has generated risk-based, exposure-related guidelines designed to direct the follow-up care of survivors of pediatric malignancies.	• This article expands on the guidelines by reviewing the risk factors for the development of neurocognitive sequelae and describing the expected pattern of these disabilities. • Presents recommendations for the screening and management of neurocognitive late effects and outline important areas of school and legal advocacy for survivors with disabilities.
Nazemi KJ, Butler RW. Neuropsychological rehabilitation for survivors of childhood and adolescent brain tumors: a view of the past and a vision for a promising future. J Pediatr Rehabil Med. 2011;4:37-46.	7	NA	Recent advances and current approaches in treatment interventions for neuropsychological sequelae are reviewed	• There is an acute need for further advances in this field, and a bright future of individualized school re-integration is within reach.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Netson KL, Conklin HM, Ashford JM, Parent and teacher ratings of attention during a year-long methylphenidate trial in children treated for cancer. J Pediatr Psychol. 2011;36:438-50.	4b	33 with ALL and 35 with BT who completed a 12-month, open-label trial of MPH	To longitudinally examine attention performance in survivors prescribed MPH to ameliorate cognitive late effects, comparing measures for inter-rater and inter-method discrepancies	• Survivors' attention improved after 1 month on MPH, with relative stability throughout the trail. Inter-rater agreement between parents and teachers was low to moderate. • Observer ratings correlated with select CPT indices at baseline but not at 12 months.
Netson KL, Conklin HM, Wu S, et al. A 5-year investigation of children's adaptive functioning following conformal radiation therapy for localized ependymoma.Int J Radiat Oncol Biol Phys. 2012;84:217-223.e1.	4a	123 children with intracranial ependymoma	Longitudinal investigation prospectively examined intelligence quotient (IQ) and adaptive functioning during the first 5 years after irradiation in children diagnosed with ependymoma	• Baseline IQ and VABS were below normative means, although within the average range. • Linear mixed models revealed stable IQ and VABS across the follow-up period. • Annual change in IQ did not correlate with annual change in VABS. • Clinical factors associated with poorer baseline performance included pre-irradiation chemotherapy, cerebrospinal fluid shunt placement, number and extent of surgical resections, and younger age at treatment. • No clinical factors significantly affected the rate of change in scores.
Netson KL, Conklin HM, Wu S, et al. Longitudinal investigation of adaptive functioning following conformal irradiation for pediatric craniopharyngioma and low-grade glioma.Int J Radiat Oncol Biol Phys. 2013;85:1301-6.	4b	62 children with craniopharyngioma and 77 with low-grade glioma (LGG)	Longitudinal investigation prospectively examined intellectual and adaptive functioning during the first 5 years following irradiation for childhood craniopharyngioma and low-grade glioma (LGG)	• Baseline assessment revealed no deficits in IQ and VABS indices for children with craniopharyngioma, with significant ($P < .05$) longitudinal decline in VABS Communication and Socialization indices. • Clinical factors associated with more rapid decline included females and pre-irradiation chemotherapy (interferon). • Older age at irradiation was a protective factor against longitudinal decline.
Northman L, Ross S, Morris M, et al. Supporting pediatric cancer survivors with neurocognitive late effects: a model of care. J Pediatr Oncol Nurs. 2015;32:134-42.	7	NA	Provides an overview of the School Liaison Program model of care and discusses parent-perceived quality and program effectiveness	
Notteghem P, Soler C, Dellatolas G, et al. Neuropsychological outcome in long-term survivors of a childhood extracranial solid tumor who have undergone autologous bone marrow transplantation. Bone Marrow Transplant. 2003;31:599-606.	4a	76 children treated for an extracranial tumor with SCT without TBI, assessed > 5 years post-SCT	Evaluate the neuropsychological and adaptive functioning of children who underwent SCT	• IQ in average range and not significantly different from normative values. • Academic achievement, and later vocational achievement were also within normal levels. • A subset who had hearing loss related to prior use of cisplatin showed lower verbal IQ. • A subset who had prolonged school absence showed significantly impaired reading scores.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Özyurt J, Thiel CM, Lorenzen A, et al. Neuropsychological outcome in patients with childhood craniopharyngioma and hypothalamic involvement. J Pediatr. 2014;164:876-881.	4c	15 patients with childhood craniopharyngioma and known hypothalamic involvement & 24 age- and IQ matched controls	Test memory performance and executive functions in patients with childhood craniopharyngioma and hypothalamic involvement	• Patients demonstrated significantly lower performance scores in tests of memory and executive functioning. • On the individual performance level, delayed recall performance was severely impaired in one-third of the patients. • Compared with patients with low-grade hypothalamic involvement, those with high-grade hypothalamic involvement showed worse performance in executive functions and reduced functional capabilities for daily life actions, indicating lower quality of life
Palmer SL, Armstrong C, Onar-Thomas A, et al. Processing speed, attention, and working memory after treatment for medulloblastoma: an international, prospective, and longitudinal study. J Clin Onc, 2013;31:3494-500.	4a	125 (3-21 years at dx) medulloblastoma	Prospectivepostsurgical risk-adapted craniospinalirradiation-(n = 36 high risk [HR]; n = 90 average risk) 1, 3 5 years after dx • AR 23.4 Gy + 55.8 Gy boost • HR 39.6 Gy + 55.8 boost	• Children completed 509 neuropsychological evaluations using the Woodcock-Johnson Tests of Cognitive Abilities Third Edition • Median of three observations per patient • Linear mixed effects models revealed that younger age at diagnosis, HR classification, and higher baseline scores were significantly associated with poorer outcomes in processing speed • Patients treated as HR and those with higher baseline scores are estimated to have less favorable outcomes in working memory and broad attention over time • Parent education and marital status were significantly associated with broad attention and working memory baseline scores but not change over time
Palmer SL, Hassall T, Evankovich K, et al. Neurocognitive outcome 12 months following cerebellar mutism syndrome in pediatric patients with medulloblastoma. Neuro Oncol. 2010;12:1311-7.	4a	44 Children with embryonal tumors, were diagnosed with postoperative +/-CMS	Prospectively assess early neurocognitive outcome of children who developed cerebellar mutism syndrome (CMS) following surgical resection of a posterior fossa embryonal tumor, compared with carefully matched control patients	• While the matched control patients exhibited performance in the average range, patients who developed CMS postsurgery were found to have significantly lower performance in processing speed, attention, working memory, executive processes, cognitive efficiency, reading, spelling, and math
Palmer SL, Goloubeva O, Reddick WE, et al. Patterns of intellectual development among survivors of pediatric medulloblastoma: a longitudinal analysis. J Clin Oncol. 2001;19:2302-8.	4a	42 children with MB with 150 testings	To examine two competing hypotheses relating to intellectual loss among children treated for medulloblastoma (MB): Children with MB either: (1) lose previously learned skills and information; or (2) acquire new skills and information but at a rate slower than expected compared with healthy same-age peers	• A significant decline in cognitive performance during the time since XRT was demonstrated, with a mean loss of 2.55 estimated FSIQ points per year (P = .0001). • Analysis for the basis of the intelligence quotient (IQ) loss revealed that subtest raw score values increased significantly over time since XRT, but the rate of increase was less than normally expected, which resulted in decreased IQ scores. • Results supported the hypothesis that MB patients demonstrate a decline in IQ values because of an inability to acquire new skills and information at a rate comparable to their healthy same-age peers, as opposed to a loss of previously acquired information and skills

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Palmer SL, Reddick WE, Glass JO, et al. Regional white matter anisotropy and reading ability in patients treated for pediatric embryonal tumors. Brain Imaging Behav. 2010;4:132-40.	4a	54 embryonal tumors	To investigate the association between reading decoding and WM integrity	• Decoding increased with age of the patient at time of evaluation, though no difference between average and high risk. • Decoding related to DTI FA in multiple areas
Papazoglou A, King TZ, Morris RD, et al. Cognitive predictors of adaptive functioning vary according to pediatric brain tumor location. Dev Neuropsychol. 2008;33:505-20.	4a	36 children treated for brain tumors	Archival study sought to determine if the relationship between cognitive and adaptive abilities varied according to brain tumor location	• Best cognitive predictors of adaptive functioning were hypothesized to be attention span within the cerebellar group and verbal memory within the third ventricle group • Auditory attention span significantly predicted communication skills for the cerebellar group, whereas verbal memory significantly predicted socialization skills for the third ventricle group
Patel SK, Katz ER, Richardson R, et al. Cognitive and problem solving training in children with cancer: a pilot project. J Pediatr Hematol Oncol. 2009;31:670-7.	3	12 survivors (CNS cancer or Tx)	To examine the efficacy of 15 session intervention to teach problem-solving and compensation for memory and academic dysfunction	• Pre- post-test improvement on writing samples
Patel SK, Lai-Yates JJ, Anderson JW, et al. Attention dysfunction and parent reporting in children with brain tumors. Pediatr Blood Cancer. 2007;49:970-4.	4a	70 child survivors of brain tumors	Evaluated the validity of a time-efficient, standardized parent-report measure in identifying attention dysfunction in childhood brain tumor survivors	• Survivors in the attention dysfunction group were reported by their parents as having significantly more attention problems relative to the group without attention dysfunction on objective testing. • Furthermore, survivors categorized as having attention dysfunction based on their neuropsychological test scores were reported on the CBCL by their parents as having significantly more social problems
Patel SK, Lo TT, Dennis JM, et al. Neurocognitive and behavioral outcomes in Latino childhood cancer survivors. Pediatr Blood Cancer. 2013;60:1696-702.	4a	73 predominantly Spanish-speaking parents of pediatric brain tumor or leukemia survivors	Evaluated the neurocognitive and behavioral outcomes and their impact on the health-related quality of life in survivors of childhood cancer drawn from Latino families in the Los Angeles region	• 50% of the children placed at or above the "elevated" level for difficulties with attention, school-based learning, and peer relations • Younger age at diagnosis significantly predicted dysfunction in inattention, learning problems, and hyperactivity/impulsivity
Patel SK, Mullins WA, O'Neil SH, et al. Neuropsychological differences between survivors of supratentorial and infratentorial brain tumours. J Intellect Disabil Res 2011;55:30-40.	4a	Retrospective review of 70 brain tumor patients treated brain tumor 1997 and 2002	To evaluate the relationship between brain tumor location and core areas of cognitive and behavioral functioning for pediatric brain tumor survivors	• The supratentorial and infratentorial tumour location groups did not differ on measures of intellectual functioning. • However, overall pattern where survivors of intratentorial tumor performed more poorly on selected measures of more specific cognitive functions and on parent-report of social-emotional functioning relative to survivors of supratentorial tumours. • Infra did worse on attention, working memory, reading, spelling, parent report of withdrawal and anxiety-depression on CBCL. Also, higher incidence of examiner-report of behavioral problems in neuropsychological reports for children with infra relative to supra. • Higher frequency of auditory deficits was noted in the infratentorial tumour group and was associated with lowered academic achievement scores.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Patel SK, Ross P, Cuevas M, et al. Parent-directed intervention for children with cancer-related neurobehavioral late effects: A randomized pilot study. J Pediatr Psychol. 2014;39:1013-27.	3	44 cancer survivors (ages 6-18) and parents	Evaluate feasibility and efficacy of a parent-directed to improve academic functioning in childhood cancer survivors with neurobehavioral late effects	• 90% of intervention parents completed the program with high adherence/perceived benefit. Between-group effect sizes ranged from d = 0.77 to d = 1.45 for parent knowledge, efficacy, frequency of pro-learning behaviors, and d = 0.21 to d = 0.76 for child academic scores. • Parental time spent in intervention activities was associated with academic change. • A parent-directed intervention to indirectly promote academic functioning in CCSs appears feasible and effective in improving targeted parenting outcomes and for selected child academic outcomes.
Patel SK, Wong AL, Cuevas M, et al. Parenting stress and neurocognitive late effects in childhood cancer survivors. Psychooncology. 2013;22:1774-82.	4a	44 children who survived cancer involving central nervous system-directed treatments	Investigated the impact of child neurocognitive effects on parenting stress	• Parent stress was significantly associated with both performance-based and parent report measures of child executive functioning. • Child executive functioning significantly predicted parent stress even after controlling for socio-demographic and clinical factors, and the final model accounted for 42% of the variance in parent stress levels.
Pauly-Takacs K, Moulin CJ, Estlin EJ. Benefits and limitations of errorless learning after surviving pediatric brain tumors: a case study. J Clin Exp Neuropsychol. 2012;34:654-66.	4c	A 15 yo with metastatic germ cell tumor	Case study of profound episodic memory impairment	• Learning was more efficient under errorless conditions, although access to the information from long-term memory remained cue dependent.
Penn A, Lowis SP, Hunt LP, et al. Health related quality of life in the first year after diagnosis in children with brain tumours compared with matched healthy controls; a prospective longitudinal study. Eur J Cancer. 2008;44:1243-52.	4b	37 tumor patients and 42 controls	Compares parent- and self-report health-related quality of life (HRQL) in children aged 2-16 years with brain tumours, one, six and twelve months after diagnosis with matched normal controls	• The relationship between self- and parent-report in patients and controls was inconsistent; varied over time; and did not consistently correlate with parental depressive symptoms, suggesting parents and their children do not regard HRQL in a similar way
Penn A, Shortman RI, Lowis SP, et al. Child-Related Determinants of health-related quality of life in children with brain tumours 1 year after diagnosis. Pediatr Blood Cancer 2010;55:1377-85.	4b	35 children Median age at diagnosis = 9.1	To identify early child-related determinates of parent- and child-report health related quality of life in children with infratentorial tumors	• Measured participants 1 month and 12 months post diagnosis • Infratentorial tumour site predicted health-related quality of life 1 year after diagnosis. • Infratentorial tumor site and selective attention at 1 month predicted poor self- and parent-report of health related quality of life at 12 months. • No other cognitive or self-report measures predicted health related quality of life.
Perkins JL, Kunin-Batson AS, Youngren NM, et al. Long-term follow-up of children who underwent hematopoietic cell transplant (HCT) for AML or ALL at less than 3 years of age. Pediatr Blood Cancer. 2007;49:958-63.	4a	17 patients transplanted before age 3 were evaluated 3-22 years post-SCT	To examine physical, neurocognitive and quality of life outcomes in survivors who were transplanted at age < 3 years	• IQ was in average range. • Attention and executive function deficits were noted in many survivors. • No differences in mean QOL levels compared to population norms. • Even in very young patients transplanted with TBI, most are functioning in the average range.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
PetersonCC, Johnson CE, Ramirez LY, et al. A meta-analysis of the neuropsychological sequelae of chemotherapy-only treatment for pediatric acute lymphoblastic leukemia. Pediatr Blood Cancer. 2008;51:99-104.	1	13 articles	Meta-analysis assessing neuropsychological and academic functioning differences between children with ALL treated solely with chemotherapy and comparison groups	• Mean effect sizes were significantly different from zero for multiple domains of intelligence and academic achievement; processing speed; verbal memory; and some aspects of executive functioning and fine motor skills, indicating worse functioning in ALL survivors. • Effect sizes for visual-motor skills and visual memory were not significantly different from zero.
Phipps S, Dunavant M, Srivastava DK, et al. Cognitive and academic functioning in survivors of pediatric bone marrow transplantation. J Clin Oncol. 2000;18:1004-11.	4a	Children assessed pre-SCT and at 1-yr (n = 102) and 3-yrs (n = 54) post-SCT (from cohort of 260 assessed pre-SCT	Examine cognitive and psychoeducational outcomes of children undergoing SCT in a prospective, longitudinal design	• In cohort as a whole, no significant declines in IQ or academic achievement at 1 or 3 years post-SCT. • Age a significant predictor, with patients < 3 years showing significant decline over time. • TBI not related to outcome. • Concludes that SCT, even with TBI entails minimal risk of neurocognitive impairment in patients < 6 years, but younger children may be at some risk.
Phipps S, Rai SN, Leung WH, et al. Cognitive and academic consequences of stem cell transplantation in children. J Clin Oncol. 2008;26:2027-33.	4a	158 children who underwent SCT, survived and provided at least 1 post-SCT assessment (of 268 assessed pre-SCT). Follow-up of entire cohort to 5-yrs post-SCT	Examine cognitive and psychoeducational outcomes of children undergoing SCT in a prospective, longitudinal design. Same cohort as above study, with complete follow-up through 5 years post-SCT	• In cohort as a whole, no changes observed in global IQ and academic achievement. • Differences in longitudinal trajectory based on diagnosis, type of transplant, use of TBI, and presence of graft vs. host disease (gvhd). • Age was no longer a significant determinant of outcome. • Children who received TBI showed a significant decline in IQ, but only the equivalent of 3 IQ points in 5 years. • Differences based on socioeconomic status (SES) were much larger, and dwarfed that of other significant predictor variables.
Phillips SM, Padgett LS, Leisenring WM, et al. Survivors of childhood cancer in the United States: prevalence and burden of morbidity. Cancer Epidemiol Biomarkers Prev. 2015;24:653-63.	4a	388,501 survivors of childhood cancer	Updated prevalence estimates of childhood cancer survivors as of 2011 and burden of morbidity in this population	• Prevalence of any chronic condition among ≥5-year survivors ranged from 66% (ages 5-19) to 88% (ages 40-49). • Estimates for specific morbidities ranged from 12% (pain) to 35% (neurocognitive dysfunction).
Protas PT, Muszynska-Roslan K, Holownia A, et al. Cerebrospinal fluid changes in the excitatory amino acids concentration caused by the standard treatment of acute lymphoblastic leukaemia in children do not correlate with their later cognitive functioning. Neuropediatrics. 2009;40:295-7.	4a	12 ALL pts; M age of diagnosis 7.41; M time since dx 3.7	To assess the correlation between glutamate and aspartate concentrations (as key excitatory amino acids) in the CSF and cognitive functioning in ALL children	• Found a statistically significant increase in glutamate and aspartate in 12 ALL patients during their treatment. • IQ functioning was examined in all patients at an average of 3.7 years after the disease diagnosis. • IQ Mean scores all in the average range, and did not significantly correlate with glutamate or aspartate concentrations at any of the time points for which these were collected.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Protas PT, Muszynska-Roslan K, Holownia A, et al. Negative correlation between cerebrospinal fluid tau protein and cognitive functioning in children with acute lymphoblastic leukemia. Pediatr Blood Cancer. 2009;53:105-8.	4a	38 children assessed an average of 3.7 years after diagnosis	Assess whether cerebrospinal fluid tau protein is associated with cognitive changes in children with acute lymphoblastic leukemia (ALL)	• Level of tau at the initiation of maintenance therapy was negatively correlated with verbal abilities measured on Wechsler intellectual scale.
Puget S, Boddaert N, Viguier D, et al. Injuries to inferior vermis and dentate nuclei predict poor neurological and neuropsychological outcome in children with malignant posterior fossa tumors. Cancer. 2009;115:1338-47.	4a	61 children with posterior fossa tumors (PFT) M age at time of testing = 6.0 Testing took place M = 5.6 years post diagnosis	Find the correlation between anatomical brain damage due to PFT and neurological/ neuropsychological functioning in children who have completed treatment (surgery, chemo., XRT) for PFT	• Neurological deficits predicted low cognitive performance, irrespective of other risk factors. • Cerebellar deficits and fine motor dexterity impairment was correlated with damage to the dentate nuclei and inferior vermis. (Not correlated with middle or superior vermis). • FSIQ scores were inversely correlated with the severity of damage to the dentate nuclei. • FSIQ scores correlated with severity of cerebellar deficits. • Fine motor scores correlated with IQ.
Qaddoumi I, Ellison DW, Morris EB, et al. Dysembryoplastic neuroepithelial tumors and cognitive outcome: cure at a price? Cancer. 2010;116:5461-9.	4a	11 children with Dysembryoplastic neuroepithelial tumors (DNETs) Median age at diagnosis = 10 Neuropsych testing done "at least once during follow-up" (i.e. no uniform time)	To document the clinical features, neurocognitive function, and treatment outcomes of 11 children diagnosed with DNETs	• 67% of participants had a visual field deficit. • Only 3 participants demonstrated normal or above normal intellectual functioning. • 63% of children were eligible (or were receiving) receive special services in school. • Found higher rate of DNET recurrence than other studies. Not necessarily a benign course despite general view that the DNET's are benign tumors.
Reddick WE, Shan ZY, Glass JO, et al. Smaller white-matter volumes are associated with larger deficits in attention and learning among long-term survivors of acute lymphoblastic leukemia. Cancer. 2006;106:941-9.	4a	112 ALL survivors	Test the hypothesis that survivors of childhood acute lymphoblastic leukemia (ALL) have deficits in neurocognitive performance, and smaller white-matter volumes are associated with these deficits	• Most performance measures demonstrated statistically significant differences from normative test scores, but only attention measures exceeded 1.0 standard deviation from normal. • Patients who had received chemotherapy alone had significantly larger volumes of white matter than patients who had received treatment that also included cranial irradiation.
Reddick WE, Taghipour DJ, Glass JO, et al. Prognostic factors that increase the risk for reduced white matter volumes and deficits in attention and learning for survivors of childhood cancers.Pediatr Blood Cancer. 2014;61:1074-9.	4c	383 childhood cancer survivors (199 ALL, 184 BT) at least 12 months post-completion of therapy and 67 healthy siblings	A prospective validation of the purported reduction in WMV, associated influential factors, and its relationship to neurocognitive deficits in a very large cohort of both acute lymphoblastic leukemia (ALL) and malignant brain tumors (BT) survivors in comparison to an age similar cohort of healthy sibling controls	• BT survivors had lower WMV than ALL survivors, who had less than the control group. • Increased CNS treatment intensity, younger age at treatment, and greater time since treatment were significantly associated with lower WMV. • Cancer survivors did not perform as well as the control group on neurocognitive measures of intelligence, attention, and academic achievement. • Reduced WMV had a larger impact on estimated IQ among females and children treated at a younger age.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Reeves CB, Palmer SL, Reddick WE, et al. Attention and memory functioning among pediatric patients with medulloblastoma. J Pediatr Psychol. 2006;31:272-80.	4a	38 child survivors of MB	Test the hypotheses that memory and attention deficits are prevalent in survivors of childhood medulloblastoma (MB) and that these deficits are associated with problems with academic achievement	• No significant verbal memory deficits were found. • 8 of 11 CPT variables were significantly below the standardization mean.
Reimers TS, Mortensen EL, Nysom K, et al. Health-related quality of life in long-term survivors of childhood brain tumors. Pediatr Blood Cancer. 2009;53:1086-91.	4a	126 childhood brain tumor patients M age of diagnosis = 8.3 M age of follow up = 21 (range 8 to 40 years)	To identify predictors for health-related quality of life in survivors of childhood brain tumors and its relationship to cognitive function	• Treatment with radiation therapy predicted reduced health-related quality of life. However, when IQ introduced as a covariate, IQ partially mediated the relationship. • Treatment with radiation therapy predicted lower physical functioning/energy, social functioning, cognitive functioning, body image, outlook of life, and intimate relations. • Age at diagnosis associated with lowered scores for social functioning, while age at follow up was associated with more physical symptoms. • Tumor location in the posterior fossa associated with lowest scores for physical functioning and energy. • Tumor location in the 3rd ventricle region was associated with lower scores for body image. • Authors concluded that Radiation therapy is an important predictor of HRQOL primarily due to its effect on general IQ, which suggests that IQ is a strong determinant of HRQOL.
Riggs L, Bouffet E, Laughlin S, et al. Changes to memory structures in children treated for posterior fossa tumors.J IntNeuropsychol Soc. 2014;20:168-80.	4a	20 pediatric survivors of MB and one survivor of astrocytoma treated with cranial-spinal radiation and 13 healthy controls	Examined the effects of treatment on measures of *global* brain structure (i.e., total white and gray matter volume) and *specific* memory structures (i.e., hippocampus and uncinate fasciculus)	• Performance on the general index of the CMS was significantly correlated with measures of hippocampal volume and uncinate fasciculus.
Robinson KE, Kuttesch JF, Champion JE, et al. A quantitative meta-analysis of neurocognitive sequelae in survivors of pediatric brain tumors. Pediatr Blood Cancer. 2010;55:525-31.	1	1,318 children in 39 empirical studies M age at time of testing = 11.1 M age at time of diagnosis = 6.1 M time elapsed since treatment = 4.1	To provide a comprehensive meta-analysis of the literature on long-term neurocognitive late effects found in survivors of pediatric brain tumors	• Overall effect size of late-effect cognitive deficits – 0.91 • By neurocognitive domain, effect sizes ranged from -0.45 to -1.43. • Overall Cognitive Functioning: -.083. • Academic Achievement: -0.45 thru -0.63. • Attention/Concentration: -1.22. • Psychomotor Skill: -1.43. • Verbal Memory: -1.14. • Visuospatial Skill:-1.14. • Language:-.92.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Robinson KE, Livesay KL, Campbell LK, et al. Working memory in survivors of childhood acute lymphocytic leukemia: functional neuroimaging analyses. Pediatr Blood Cancer. 2010;54:585-90.	4c	8 ALL Survivors and 7 HC M age of assessment = 14.07 M age of diagnosis = 4.94 M yrs post treatment = 6.46	To use functional neuroimaging to examine working memory and executive functioning deficits of survivors of childhood acute lymphocytic leukemia, as compared to age- and gender-matched health controls	• There was a trend for ALL survivors to perform more poorly than HC's on working memory (specifically overall accuracy). • Survivors had greater activation in areas related to working memory (dorsolateral and ventrolateral prefrontal cortex) and error monitoring (dorsal and ventral anterior cingulated cortex). • Authors indicate their findings support the theory of compensatory activation in necessary brain regions in order to complete tasks in pediatric ALL survivors.
Robinson KE, Pearson MM, Cannistraci CJ, et al. Neuroimaging of executive function in survivors of pediatric brain tumors and healthy controls. Neuropsychology. 2014;28:791-800.	4b	17 pediatric brain tumor survivors and 15 healthy controls	Identification of specific neurobiological mechanisms of neurocognitive deficits using neuroimaging techniques	• Survivors of pediatric brain tumors performed more poorly than healthy children on measures of overall cognitive ability, attention, and executive function during testing, as well as on a working memory task during fMRI.
Robinson KE, Pearson MM, Cannistraci CJ, et al. Functional neuroimaging of working memory in survivors of childhood brain tumors and healthy children: Associations with coping and psychosocial outcomes. Child Neuropsychol. 2014 Jun 5:1-24. [Epub ahead of print]	4b	17 pediatric brain tumors; age 8-16) and 15 healthy children	Questionnaire measures and functional neuroimaging were used to examine the neurocognitive, psychosocial, and emotional functioning and coping responses of survivors of pediatric brain tumors	• Survivors experienced elevated levels of psychosocial and behavioral/emotional difficulties relative to healthy controls and normative data. • Increases in brain activation in prefrontal and other anterior regions in response to a working memory task were associated with better psychosocial functioning, use of engagement coping strategies, and less use of disengagement coping strategies. • Regression analyses suggest coping accounts for a significant portion of the association between brain activation and behavioral/emotional functioning.
Robinson KE, Wolfe KR, Yeates KO, et al. Predictors of adaptive functioning and psychosocial adjustment in children with pediatric brain tumor: a report from the Brain Radiation Investigative Study Consortium. Pediatr Blood Cancer. 2015;62:509-16.	4a	56 diagnosed with a pediatric brain tumor	Examined whether familial/demographic, developmental, diagnostic, or treatment-related variables best predict the acute psychosocial adjustment and adaptive functioning	• Parent ratings of behavioral symptoms and adaptive functioning were within normative expectation, although rates of clinical impairment in adaptive functioning exceeded expected rates.
Rønning C, Sundet K, Due-Tønnessen B, et al. Persistent cognitive dysfunction secondary to cerebellar injury in patients treated for posterior fossa tumors in childhood. Pediatr Neurosurg. 2005;41:15-21.	4c	12 young adults that had been treated for astrocytoma with surgery alone; 11 young adults treated of medulloblastoma group	Determine the neuropsychological profile of young adults treated for a posterior fossa tumor in childhood and look for possible support for the presence of the so-called 'cerebellar cognitive affective syndrome'	Medulloblastoma group performed poorer than the astocytoma group on all neuropsychological measures except one. The astrocytoma group also had impaired scores compared with standard norms on measures of motor speed, attention and executive function. No significant correlation between age at time of treatment and grade of neuropsychological impairment was found in the astrocytoma group, though there was a tendency that young age at time of treatment correlated with better outcome on IQ measures.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Rueckriegel SM, Blankenburg F, Henze G, et al. Loss of fine motor correlates with ataxia and decline of cognition in cerebellar tumor survivors. Pediatr Blood Cancer. 2009;53:424-31.	4c	25 medulloblastoma and 16 cerebellar pilocytic astrocytoma pts 187 HC; Age at evaluation 13.2 (PA) & 14.9 (MB); Age at therapy 10.0 (PA) & 9.3 (MB); Time post-treatment 35.5 mo (PA) & 51 mo (MB)	Find the association between loss of fine motor function and ataxia and intelligence in pt's 1+ year post-treatment with and without adjuvant treatment. Used a digitizing graphic tablet to measure different movement complexity levles	• MB pts impaired for both simple and complex fine motor skills. • PA pts normal for simple and impaired for complex fine motor. • Fine motor Function associated with Ataxia for both groups, but more so with MB pts. • Young age and short recovery time correlated significantly with impaired kinematic parameters. • Fine motor function associated with IQ, particularly Performance IQ.
Rueckriegel SM, Bruhn H, Thomale UW, et al. Cerebral white matter fractional anisotropy and tract volume as measured by MR imaging are associated with impaired cognitive and motor function in pediatric posterior fossa tumor survivors. Pediatr Blood Cancer. 2015;62:1252-8.	4a	18 medulloblastoma survivors	Tested whether damage to white matter (WM) as revealed by diffusion tensor MR imaging (DTI) correlated with specific cognitive and motor impairments in survivors of pediatric posterior fossa tumors	• The WM/GM+ CSF ratio correlated significantly with cognitive measures (IQ, ANT baseline speed; ANT shifting attention). • Frontocerebellar tract volumes correlated with FSIQ.
Saury JM, Emanuelson I. Cognitive consequences of the treatment of medulloblastoma among children. Pediatr Neurol. 2011;44:21-30.	4a	8 pediatric survivors of medulloblastoma	Multiple assessments of 8 pediatric survivors of medulloblastoma treatment with surgery, radiation, and chemotherapy	• Slower acquisition of functions and knowledge in the domains of verbal comprehension, perceptual organization, social perception, and psychomotor skills.
Sands SA, Oberg JA, Gardner SL, et al. Neuropsychological functioning of children treated with intensive chemotherapy followed by myeloablative consolidation chemotherapy and autologous hematopoietic cell rescue for newly diagnosed cns tumors: an analysis of the Head Start II survivors. Pediatr Blood Cancer. 2010;54:429-36.	4a	49 pts with malignant brain tumor 26 survivors tested at 3 years post-treatment M age of diagnosis = 2.9 T2 approx 3 years post diagnosis	To evaluate the neuropsychological late effects amongst survivors treated on the Head Start II protocol between 1997 and 2003. (Craniospinal irradiation was avoided in 2/3's of patients. Protocol includes AuHCT.)	• From T1 to T2 mean VIQ, PIQ, Reading, Spelling, Math, and Receptive Language drop from the Average to the Low Average range. • From T1 to T2 mean FSIQ, VMI stay in the Low Average range. • From T1 to T2 Learning and Memory either maintains (in the Average range) or increases (from Low Average to Average). • Parent-reported socio-emotional functioning within normal limits. • Serial testing found FSIQ to be stable over 3 year follow up. • The authors assert that the Head Start II protocol helps minimize neurocognitive late effects. • Continue follow up in necessary to determine the preservation of neurocognitive functioning.
Sands SA, Zhou T, O'Neil SH, et al. Long-term follow-up of children treated for high-grade gliomas: children's oncology group L991 final study report. J Clin Oncol. 2012;30:943-9.	4a	54 patients with high-grade gliomas	Investigated the neuropsychological, behavioral, and quality of life (QoL) outcomes after treatment on the Children's Cancer Group (CCG) trial for high-grade gliomas (CCG-945)	• Average follow-up time of 15 years. • Survivors demonstrated intellectual functioning within the low-average range. • Executive functioning and verbal memory were between the low-average and borderline ranges.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Schmidt AT, Martin RB, Ozturk A, et al. Neuroimaging and neuropsychological follow-up study in a pediatric brain tumor patient treated with surgery and radiation. Neurocase. 2010;16:74-90.	5	2 case reports	Present neuropsychological, magnetic resonance imaging, proton magnetic resonance spectroscopic imaging, and diffusion tensor imaging data for two adolescents (one patient with ependymal spinal cord tumor with intracranial metastases, and one healthy, typically developing control) from three time points	• Progressive decreases in gray and white matter volumes as well as early decreases in mean N-acetyl aspartate/choline (NAA/Cho) ratios and fractional anisotropy (FA) in regions with normal appearance on conventional MRI. • At the last follow-up, NAA/Cho and FA tended to change in the direction to normal values in selected regions. • A patient had initial reduction in language and motor skills, followed by return to baseline, but later onset delay in visuospatial and visual perceptual skills.
Schreiber JE, Gurney JG, Palmer SL, et al. Examination of risk factors for intellectual and academic outcomes following treatment for pediatric medulloblastoma. Neuro Oncol. 2014;16:1129-36.	4a	165 patients (ages 3-21 years) treated with surgery, risk-adapted craniospinal irradiation, and 4 courses of chemotherapy with stem cell support	Prospectively examine the effects of hearing loss and posterior fossa syndrome (PFS)	• Serious hearing loss, PFS, younger age at diagnosis, and high-risk status were all significant risk factors for decline in intellectual and academic skills. • Serious hearing loss and PFS independently predicted below-average estimated mean intellectual ability at 5 years post diagnosis. • Patients with high-risk medulloblastoma and young age at diagnosis (<7 years) exhibited the largest drop in mean scores for intellectual and academic outcomes.
Schubert T, Trippel M, Tacke U, et al. Neurosurgical treatment strategies in childhood craniopharyngiomas: is less more? Childs Nerv Syst. 2009;25:1419-27.	4c	32 total 17 w microsurgical resection, 7 with stereotactic cyst drainage and radiotherapy, and 8 with combined approaches M age of diagnosis = 8.1 M follow-up = 5.5 yrs	To retrospectively analyze different treatment methods for craniopharyngiomas, particularly related to the extent to which the tumor is controlled, as well as clinical outcomes	• Stereotactic cyst punction ○ 6/7 still alive ○ 7/7 in "age appropriate neuropsychological condition" ○ 2/7 have tumor recurrence • Microsurgical resection ○ 15/17 are alive ○ 10/17 have "age appropriate neuropsychological development) ○ 14/17 have tumor recurrence • Authors assert that pts treated with less invasive (i.e. steroetactic and radiotherapeutical methods) have a more favorable long-term clinical outcomes (both regarding survival, recurrence, and neuropsychological functioning) compared to children treated with a more radical microsurgical approach.
Schulte F, Bartels U, Bouffet E, et al. Body weight, social competence, and cognitive functioning in survivors of childhood brain tumors. Pediatr Blood Cancer. 2010;55:532-39.	4a	54 survivors of childhood brain tumors M age at time of testing = 13.7 M age of diagnosis = 7.4 M time since treatment = 5.7	To examine the association of BMI with social competence and cognitive function, as well as the congruency in reporting of survivors' social competence by the survivors, parents, and teachers	• Survivors were more underweight and less overweight than population norms. • Parents perceived lower social competence in survivors that were under weight—they also had lower VIQ and higher internalizing behaviors. • Survivors with lower weight and lower IQ perceived having fewer close friendships. • Survivor, parent, and teacher reports were moderately congruent.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Shortman RI, Beringer A, Penn A, et al. The experience of mothers caring for a child with a brain tumour. Child Care Health Dev. 2013;39:743-9.	5	6 mothers	(1) To explore the impact of having a child with a brain tumour on the main caregiver in the family; (2) to describe mothers' experiences of coping with their child's illness, including personal barriers and strengths; and (3) to identify causes of stress and sources of support to inform improvements in care delivery	• Families selected for 1:1 interview based upon scores on the IFS. • Caregivers in the high-impact group reported less conflict. • High and medium-impact group caregivers had experienced less 'hindrance and heartache', than those with low impact scores, suggesting that the stress associated with diagnosis and treatment of the tumour may have increased cohesion and acceptance within these families.
Shortman RI,Lowis SP,Penn A, et al. Cognitive function in children with brain tumors in the first year after diagnosis compared to healthy matched controls.Pediatr Blood Cancer. 2014;61:464-72.	4b	48 children 2-16 years + matched controls	Aims were to 1) investigate cognition in children with primary BTs 1, 6, and 12 months post-diagnosis compared with healthy children 2) exploring the impact of disease and treatment variables	• Cognition was assessed using age-appropriate Wechsler Intelligence scales; Children's Memory Scale; Test of Everyday Attention for Children, and Wechsler Quicktest. • Patients with BTs had significantly reduced performance compared to controls early post-diagnosis in tests of Performance IQ, processing speed, verbal and visual memory, and selective attention. • Improved performance over 12 months was seen in patients with BTs although also, for some measures, in controls. Significant deficits in cognitive performance were seen one year post-diagnosis for Verbal IQ; processing speed, visual and verbal immediate memory, and selective attention. • Infratentorial site, high tumor grade, hydrocephalus, radiotherapy, and chemotherapy were associated with poorer functioning.
Simms S, Kazak AE, Golumb V, et al. Cognitive, behavioral and social outcome in survivors of childhood stem cell transplantation. J Pediatr Hematol Oncol. 2002;24:115-19.	4a	47 children assessed pre-, 1-yr, and 2-yrs post-SCT (from cohort of 238 assessed pre-SCT)	Examine cognitive and psychoeducational outcomes of children undergoing SCT in a prospective, longitudinal design	• No significant changes in any cognitive or academic achievement measures at 1 or 2 years post-SCT. • No difference between TBI and non-TBI regimens. • Children < 3 years showed poorer cognitive function both pre- and post-SCT. • No evidence of decline overall, but suggestive of higher risk for younger children. • Despite absence of decline, parents of survivors perceive greater difficulties in school functioning.
Shah AJ, Epport K, Azen C, et al. Progressive declines in neurocognitive function among survivors of hematopoietic stem cell transplantion for pediatric hematologic malignancies. J Pediatr Hematol Oncol. 2008;30:411-18.	4b	38 children assessed pre-SCT and 1-yr post-SCT, with 23 assessed at 3-yrs post-SCT and 12 at 5-yrs post-SCT. Also included a healthy sibling comparison group	Examine neurocognitive outcomes of children undergoing SCT in a prospective, longitudinal design	• Patients at pre-SCT did not differ from siblings in IQ and other cognitive indices, but did have marginally lower academic achievement scores. • An inconsistent pattern of declines seen at 1, 3, & 5 yrs post-SCT. • At 5-yrs post-SCT, there were significant declines in Verbal and Performance IQ, though not Full Scale IQ. • Declines in memory scores were more pronounced. • Those patients who had TBI or cranial radiation showed greater declines, while those without either showed stable outcomes. • Limitations in the statistical approach make it difficult to appreciate the nature of change over time.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Smedler AC, Winiarski J. Neuropsychological outcome in very young hematopoietic SCT recipients in relation to pretransplant conditioning. Bone Marrow Transplant. 2008;42:515-22.	4a	22 children who underwent SCT at < 42 months of age were assessed a mean of 6.5 yrs post-SCT	To investigate whether very young children who received chemotherapy based SCT conditioning only (n = 10) have a more favorable neurocognitive outcome than those who received TBI (n = 12)	• Those who received TBI had lower Verbal and Full-Scale IQ than the chemotherapy only group. • TBI was also associated with lower Visual-Motor scores, and motor functioning. • Both groups had a high percentage showing mild to moderate deficits in attention and memory skills, but the TBI showed poorer overall outcomes. • 10 of 12 in the TBI group received a single dose of 10 Gy radiation, an approach that is no longer in common use.
Smithson EF, Phillips R, Harvey DW, et al. The use of stimulant medication to improve neurocognitive and learning outcomes in children diagnosed with brain tumours: a systematic review. 2013;49:3029-40.	1	7 full text articles reporting trials on 226 participants across 4 initial RCT recruitment samples	To evaluate results of relevant trails in order to identify those children most likely to benefit from stimulants	• Promising results shown for use of MPH in improving attention, processing speed, cognitive flexibility, and social skills (largely parent and teacher report; changes on standardized measures of academic attainment did not reach statistical significance). • Low rate of side effects (5∼10%). Mainly related to sleep, appetite, and mood. Ameliorated with reduction or discontinuation of MPH. • Factors related to better response: male, reporting greater problems at baseline, older age when treated, higher baseline IQ.
Spiegler BJ, Bouffet E, Greenberg ML, et al. Change in neurocognitive functioning after treatment with cranial radiation in childhood. J Clin Oncol. 2004;22:706-13.	4a	34 children treated for malignant PF tumors were observed with serial clinical neuropsychologic assessments	Evaluate the pattern of stability and change over time across multiple domains of neurocognitive function in radiated survivors of posterior fossa (PF) tumors	• Results showed a 2- to 4-point decline per year in intelligence scores. • For our relatively young sample, intellectual function declined quickly in the first few years after treatment, and then more gradually. • Significant declines in visual-motor integration, visual memory, verbal fluency, and executive functioning were also documented. • No decline was evident for verbal memory and receptive vocabulary.
Spiegler BJ, Kennedy K, Maze R, et al. Comparison of long-term neurocognitive outcomes in young children with acute lymphoblastic leukemia treated with cranial radiation or high-dose or very high-dose intravenous methotrexate. J Clin Oncol. 2006;24: 3858-64.	4a	79 high-risk ALL (retrospective cohort)	To compare long-term neurocognitive outcomes of high-risk ALL patients treated on a uniform chemotherapy protocol with one of three modalities of CNS prophylaxis, depending on the treatment era. The three comparison groups were treated with either: 1. 18 Gy CRT 2. HD- IV MTX, or 3. Very HD IV MTD	• The Chemotherapy only group performed significantly better than the CRT group on 17/18 of the neurocognitive measures used in this study. • In comparison with population-normative data, mean scores for the CRT group were significantly lower for 8 out 18 measures. • In contrast, the Chemotherapy-only group did not differ significantly from population means on 17 of 18 measures. • The study confirmed the deleterious effect of 18 Gy CRT in young children (under 5yrs), and suggests that high-dose IV MTX combined with IT chemotherapy is relatively benign. • The authors present the limitations of the study, and speculate on the possible mitigating effects of leucovorin rescue on the impact of IV MTX dose and neurocognitive outcomes.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Stenzel SL, Krull KR, Hockenberry M, et al. Oxidative stress and neurobehavioral problems in pediatric acute lymphoblastic leukemia patients undergoing chemotherapy. J Pediatr Hematol Oncol. 2010;32:113-8.	4a	87 children with ALL	To examine the potential relation between PC markers of oxidative stress and acute neurobehavioral outcomes in children undergoing chemotherapy	• Oxidized and unoxidized components of phosphatidylcholine (PC) were measured in the cerebrospinal fluid of 87 children with ALL at diagnosis. PC measurements were averaged to represent a induction PC mean as well as consolidation PC. • Parent report BASCs were collected at 2 time points – post consolidation and at end of therapy. • Patients were clustered into groups of high vs low physiologic reactivity and high vs low pathology on the BASC. • Results revealed a significant association between physiologic reactivity (high vs. low PC changes from diagnosis) and behavioral outcomes (high vs. low pathology). • High PC change was predictive of increased problems with aggression at the end of therapy as well as post consolidation adaptability.
Thompson SJ, Leigh L, Christensen R, et al. Immediate neurocognitive effects of methylphenidate on learning-impaired survivors of childhood cancer. J Clin Oncol. 2001;19:1802-8.	3	32 long-term survivors of childhood ALL or a malignant BT	Test if methylphenidate (MPH) has an objective beneficial effect on immediate performance on tests of neurocognitive functions among learning-impaired survivors of childhood acute lymphoblastic leukemia (ALL) and malignant brain tumors (BT)	• 15 patients randomized to the MPH group (17 patients randomized to placebo) had a significantly greater improvement on the CPT for sustained attention (errors of omission, but not for errors of commission (indicative of impulsiveness) nor reaction times. • A trend for greater improvement in the MPH group on a measure of verbal memory failed to reach statistical significance. • No trend was observed for MPH effectiveness in improving learning of a word association task. • No significant side effects from MPH were observed.
Tonning Olsson I, Perrin S, Lundgren J, et al. Long-term cognitive sequelae after pediatric brain tumor related to medical risk factors, age, and sex. Pediatr Neurol. 2014;51:515-21.	4a	69 pediatric brain tumor patients	Purpose was to find factors correlated with lowered IQ in a nationally representative sample of pediatric brain tumor patients referred for neuropsychologic evaluation	• Patients had generally suppressed IQ and impairments in executive function, memory, and attention. Lowered IQ was associated with young age at diagnosis, being male, tumor size, and treatment with whole-brain radiation therapy. • Tumor size was found to be a better predictor of cognitive sequelae than sex.
Turner CD, Chordas CA, Liptak CC, et al. Medical, psychological, cognitive and educational late- effects in pediatric low-grade glioma survivors treated with surgery only. Pediatr Blood Cancer. 2009;53:417-23.	4a	60 Low-grade glioma survivors treated with surgery only. Med age of diagnosis = 16.3 Med time since dx = 8.4	To describe the multidimensional late-effects of pediatric LGG survivors treated exclusively with surgery	• 85% of had at least one medical late-effect or psychological issue during the most recent visit, 28% had three or more. • 72% had documented medical late effects (motor dysfunction, ataxia, endocrinopathies, seizures, vision and speech problems); • 43% had one or more ongoing psychosocial problems; • 35% had FSIQ of 85 or below; more than half received sp ed services. • "Surgery-only" LGG survivors may be more affected by their tumor and its resection than previously thought.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Turner CD, Rey-Casserly C, Liptak CC, et al. Late effects of therapy for pediatric brain tumor survivors. J Child Neurol. 2009;24:1455-63.	7	NA	Review the significant late effects that occur within the medical, neurocognitive, psychosocial, and economic domains of the survivorship experience	• Late effects in different domains often coexist and can create a complex set of obstacles that pose significant challenges for a survivor of a pediatric brain tumor on a daily basis.
Ullrich NJ, Embry L. Neurocognitive dysfunction in survivors of childhood brain tumors. Semin Pediatr Neurol. 2012;19:35-42.	7	NA	Provides an overview of the types of neurocognitive deficits seen in survivors of childhood brain tumors, the tools used to assess neurocognitive function, and the factors that impact its severity	
WalshKS, Paltin I, Gioia GA, et al. Everyday executive function in standard-risk acute lymphoblastic leukemia survivors. Child Neuropsychol. 2015;21:78-89.	4a	256 SR-ALL survivors evaluated an average nine years after treatment	Evaluate parent-rated executive function (EF) in pediatric standard risk acute lymphoblastic leukemia (SR-ALL) survivors compared to a healthy comparison (HC) group	• Survivors were rated as having clinical impairments with flexibility, initiation, working memory, and emotional control at rates two to three times that of HC. • The risk of working memory and self-monitoring deficits was greater in survivors who were older when assessed. • There was no relationship between age at diagnosis or treatment regimen on EF.
Wells EM, Khademian ZP, Walsh KS, et al. Postoperative cerebellar mutism syndrome following treatment of medulloblastoma: neuroradiographic features and origin. J Neurosurg Pediatr. 2010;5:329-34.	4a	28 children treated for medulloblastoma at a single institution; referred between 1990 and 2005.	To determine factors associated with development of CMS, a means to determine its severity or cause, and outcomes of patients with this syndrome	• No sig differences in immediate post-operative MR imaging bt patients with and without CMS. • Cerebellar edema observed in 92%, there were trends for more middle and superior cerebellar peduncle edema in pts with CMS. • Pre-operative MR images showed more brainstem tumor invasion than pts without CMS. • At 1 year postoperatively, patients with CMS showed more moderate to severe atrophy/gliosis of total cerebellum ($p < 0.01$), vermis ($p < 0.01$), and brainstem ($p < 0.05$). • Neurocog available for 12/28, 5 with CMS and 7 without. Mean IQ was 16 pts lower in pts with CMS. 60% of the CMS group were receiving sp ed. Vs. 29% of those without CMS. • No association with age or sex at time of dx and development of CMS. • Authors concluded study demonstrates that CMS is associated with postoperative damage to the cerebellum and brainstem, damage not predicted by immediate postoperative MR imaging, and with poorer associated functional outcome.
Willard VW, Leung W, Huang Q, et al. Cognitive outcome after pediatric stem-cell transplantation: impact of age and total body irradiation. J Clin Oncol. 2014;32:3982-8.	4a	Of 315 patients who received SCT, 183 who were alive at 1-yr post-SCT were assessed at 1, 3, & 5 years post-SCT	To examine the influence of age and conditioning with TBI on the trajectory of cognitive functioning after SCT	• At 5-yrs post-SCT, the youngest patients (< 3 yrs) who received TBI demonstrated a significantly lower IQ than those who did not receive TBI. • Older patients showed stable cognitive trajectories regardless of TBI status. • Longitudinal analyses (using piecewise mixed-effects models with a knot at 1-yr) showed a unique pattern of change over time based on age and TBI. • The youngest patients showed a significant decline in cognitive function in the first year; however those transplanted without TBI showed subsequent gains and return to baseline by 5-yrs post-SCT. In contrast, those with TBI failed to recover first year losses, demonstrating stability in cognitive function at a lower level.

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SUPPLEMENTAL TABLE I. (*Continued*)

Study Citation	Level of Evidence*	Patients	Objective(s)	Findings
Winter AL, Conklin HM, Tyc VL, et al. Executive function late effects in survivors of pediatric brain tumors and acute lymphoblastic leukemia. J Clin Exp Neuropsychol. 2014;36:818-30.	4c	Survivors of BT (48) and ALL (50) completed neurocognitive assessment	Examine executive function late effects in survivors of pediatric brain tumors and acute lymphoblastic leukemia	• Both BT and ALL demonstrated relative executive function weaknesses. • As a group, BT survivors demonstrated weaker executive functioning than expected for age. • Those BT survivors with deficits exhibited a profile suggestive of global executive dysfunction, while affected ALL survivors tended to demonstrate specific rapid naming deficits.
Wolfe KR, Walsh KS, Reynolds NC, et al. Executive functions and social skills in survivors of pediatric brain tumor. Child Neuropsychol. 2013;19:370-84.	4a	24 survivors of pediatric brain tumor	Investigated social skills and executive functions in survivors of pediatric brain tumors	• Social functioning was related to the survivors' variability in response time, such that inconsistent responding was associated with better parent-reported and survivor-reported social skills, independent of intellectual abilities. • Additionally, parent-reported real-world global executive abilities predicted parent-reported social skills
Wolfe KR, Madan-Swain A, Kana RK. Executive dysfunction in pediatric posterior fossa tumor survivors: a systematic literature review of neurocognitive deficits and interventions. Dev Neuropsychol. 2012;37:153-75.	7	NA	Summary of studies describing executive functioning deficits in pediatric posterior fossa tumor survivors who received cranial radiation therapy and intervention studies that have targeted executive functioning deficits	• A more comprehensive model of executive functioning is proposed
Zou P, Li Y, Conklin HM, et al. Evidence of change in brain activity among childhood cancer survivors participating in a cognitive remediation program. Arch Clin Neuropsychol. 2012;27:915-29.	3	12 cancer survivors receiving treatment, 8 cancer survivor controls, 28 healthy controls	To characterize the effects of cognitive remediation on the brain's functional networks	• The CRP intervention was associated with improved attention by parent report and increased academic achievement with moderate effect sizes. CPT CCI only improved in the CRP group after remediation and there were significant difference between the CRP and survivor control group at the second time point • All participants showed improved vigilance between time of screening and 6 months later. Those who participated in the fMRI component improved in attention by parent report • After CRP treatment, small bilateral clusters in fusiform areas were detected and increased activity was detected in L ventral visual areas, cerebellum, and prefrontal cortex, suggesting that CRP may help survivors engage proper brain regions during cognitive tasks. (These findings demonstrate more normal brain patterns than seen at baseline)

*Level of Evidence: 1 = Systematic review or meta/analysis of randomized controlled trial; 2 = Randomized controlled trial; 3 = Nonrandomized controlled trial; 4 = Observational (a = cohort, b = cross/sectional, c = case/control study); 5 = Non/experimental study; 6 = Expert opinion; 7 = General review article.