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# Standard of care for neuropsychological monitoring in pediatric neuro-oncology: Lessons from the Children's Oncology Group (COG)

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## Abstract

As the mortality of pediatric cancers has decreased, focus on neuropsychological morbidities of treatment sequelae have increased. Neuropsychological evaluations are essential diagnostic tools that assess cognitive functioning and neurobiological integrity. These tests provide vital information to support ongoing medical care, documenting cognitive morbidity and response to interventions. We frame standards for neuropsychological monitoring of pediatric patients with CNS malignancy or who received cancer-directed therapies involving the CNS and discuss billing for these services in the United States (US) in the context of clinical research. We describe a cost-effective, efficient model of neuropsychological monitoring that may increases access to neuropsychological care.

### Keywords

Late effects; Pediatric oncology; Psychology

## Introduction

There are more than 270,000 survivors of childhood cancers in the United States, with approximately 11,000 children aged birth to 14 years diagnosed annually.[1] Survival rates have increased substantially over the past 40 years. Many children with cancer under age 14

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are treated on Phase III clinical research trials, which has contributed to the decline in mortality.[2,3,4]

For children with cancer, particularly those with a central nervous system (CNS) malignancy or who received cancer-directed therapies to the CNS, there has been an increased focus on monitoring neuropsychological status and functioning during and following treatment. Neuropsychological evaluation is a sensitive metric used to identify disruptions in brain-behavior relationships resulting from primary disease or associated treatment. Neuropsychological outcomes are used to identify and describe the integrity of neurobiological systems that are most vulnerable to these diseases and treatments.[5,6,7,8] Neuropsychological evaluation is a sophisticated and sensitive tool for monitoring developing brain systems and brain function both acutely and across time, much like other neurodiagnostic tests (e.g., magnetic resonance imaging [MRI], electroencephalography [EEG]).[9,10] This type of assessment provides a benchmark for functional outcomes and can be used to assess response to interventions. Changes in scores over time can be indicative of emerging late effects or early signs of disease recurrence.

In what follows, we identify the clinical importance of neuropsychological monitoring of pediatric patients with CNS malignancy or who received cancer-directed therapies involving the CNS (e.g., brain tumors, leukemia) and provide considerations for professionals who work with these populations. These diagnostic assessments to monitor functioning also provide independent information that allows clinicians to objectively classify health-related domains within the World Health Organization's (WHO) *International Classification of Functioning, Disability, and Health (ICF),* a universal classification system of disability and health.[11] Monitoring with neuropsychological assessments provides a bridge between a purely medical model and a more holistic biopsychosocial model of functioning that fits into the ICF framework.

We aim to provide evidence supporting the establishment of consistent, repeated neuropsychological monitoring of pediatric patients with CNS-associated cancers as a standard of care and to provide arguments supporting billing for insurance reimbursement for neuropsychological services provided as part of clinical research. A secondary aim is to identify challenges and advantages in implementing this approach for children and adolescents.

## Importance of Neuropsychological Monitoring

The Food and Drug Administration (FDA) has established guidelines highlighting the importance of including measures of neurodevelopment in pediatric clinical trials, specifically highlighting potential effects of certain medications on cognitive growth and development.[12] Nowhere is this more clearly relevant than in pediatric oncology. Research examining the effects of pediatric cancers and their treatments utilizing assessment of neuropsychological functioning has led to significant modifications and advances in the treatment of childhood brain tumors and acute leukemia.[13,14] The results of neuropsychological assessments in early clinical trials consistently revealed significant neurotoxicity and disability in children treated for cancers where the disease and/or

treatment involved the CNS.[15,16,17,11] These findings have played a vital role in establishing dosing schedules and alternative treatment approaches involving both chemotherapy and radiation in an attempt to diminish morbidity while maintaining increasing survival rates. As treatment protocols evolve, particularly those that aim to reduce neurotoxicity, neuropsychological monitoring (i.e., administration of repeated assessments over time) is increasingly imperative in addressing research objectives, improving clinical management, minimizing disability, and highlighting targets for potential interventions.[18]

Neuropsychological assessment in pediatric CNS-involved cancers and treatment is commonly used to evaluate ongoing functioning, late effects, and disability following treatment. Systemic neurotoxic chemotherapy, intrathecal chemotherapy, tumor resection, and cranial radiation (CRT) increase the risk for disruptions in neurodevelopment that can lead to disability.[19,20,21,5] The unfolding pattern of emerging neuropsychological deficits is unique to childhood cancers, especially CNS cancers and cancers that require CNS-targeted therapies. In contrast to other acquired injuries such as mild traumatic brain injury (TBI) or congenital developmental disorders, neuropsychological deficits in this patient population often emerge slowly and can intensify over time.[21] Early detection of deterioration in neuropsychological functioning allows earlier interventions that can moderate subsequent disability. A one-time neuropsychological assessment provides a discrete snapshot of development and functioning but does not produce adequate information on the trajectory of emerging late effects. In contrast, completing serial neuropsychological evaluations (monitoring) provides information on the onset, stability, and severity of neuropsychological disruptions and is essential in the care of this vulnerable patient population. Ideally, these assessments are conducted initially upon medical stabilization after treatment and are repeated at pre-determined intervals within the clinical research setting. An equally important benefit of neuropsychological monitoring within CNS treatment protocols is the ability to inform the clinical team about the child's health status, allowing for the triage of children whose tests suggest reduced functioning. Specifically, results from neuropsychological monitoring can indicate emerging adverse medical events affecting the child's CNS (i.e., tumor recurrence, adverse events related to chemotherapy) and can be applied clinically to develop a plan for intervention that may moderate subsequent disability. These data assist the health care team and the family in promoting the child's neuropsychological development and academic functioning. For example, assessment results can direct the course, timing, and plan of action for the child's reintegration to academic and social environments. Results can also identify deficits that may impact medical adherence, such as emerging memory or attention problems. Awareness of these deficits can lead to early recognition and intervention for emerging problems that impact daily living skills. Instability in neuropsychological functioning can also signify emergent indications of tumor recurrence or atypical side effects of therapy.

There is extensive research to support the predictive and ecological validity of a child's performance on commonly used neuropsychological measures such as intelligence tests.[22] Hence, neuropsychological assessment results frequently provide the means to infer the child's functional status in naturalistic settings. Supplementary data gathered from caregiver and teacher behavior rating scales complement data from direct child assessment, and enhance ecological validity. Combined, these data allow us to predict outcomes in such areas

as education, behavior, and social functioning to an extent that other diagnostic indicators of CNS integrity cannot (e.g., MRI, Positron Emission Tomography). Neuropsychological monitoring fits into a more holistic biopsychosocial model of care.[11]

Because common medical diagnostic assessment tools such as CT or MRI lack *functional* sensitivity, serial neuropsychological monitoring evaluations must be the routine standard of care in pediatric cancer patients with CNS malignancy or who received cancer-directed therapies involving the CNS.[23] In fact, the COG long-term follow-up guidelines for survivors of pediatric and young adult cancers recommend an initial (baseline) evaluation followed by periodic neuropsychological evaluation as clinically indicated for specific therapeutic exposures, including brain tumor resection, CRT, intrathecal chemotherapy, and specific high dose chemotherapy agents given intravenously.[24,25] As noted above, these neuropsychological monitoring evaluations bridge the medical and biopsychosocial model of care and inform clinicians and families about possible functional deficits.

## Distinction Between Neuropsychological and Psychoeducational Evaluation

Neuropsychological assessment/monitoring of pediatric cancer patients is a specialized type of evaluation provided by a licensed psychologist who is familiar with pediatric cancers. This differs from psychoeducational assessments, which are administered within the child's academic institution by a school psychologist. Unlike school-based evaluations, which focus on assessing the impact of cognitive deficits *specifically* as it relates to current academic functioning, the purpose of neuropsychological evaluation in pediatric cancer is to assess the integrity of brain-behavior relationships and the impact on all areas of functioning. Focused goals are to identify deficits and to design interventions to positively affect functioning, reduce disability, and improve quality of life for these children. The results of school-based evaluations are not routinely shared with the child's medical team and these assessments are not typically completed by a psychologist with experience in pediatric cancer or their treatments. Pediatric cancers are rare and expecting a school psychologist to have knowledge of each disease and expected functional deficits associated with various treatment modalities is not realistic. Substantial barriers preclude the school psychologist's ability to appreciate a child's trajectory of medical care and to provide the treatment team a warning when cognitive functioning is declining.

## Routine Care Costs and Reimbursement for Neuropsychological Monitoring in the Context of Research

Despite consensus that neuropsychological monitoring should be a standard of care for children with cancers involving the CNS, only about two-thirds of pediatric cancer centers currently enroll eligible patients on clinical trial protocols that include routine collection of neuropsychological assessment data on patients recently diagnosed with a malignant brain tumor.[26,27] One factor possibly limiting neuropsychological monitoring may be insufficient reimbursement for costs of conducting these assessments.

Routine care costs are expenses associated with health monitoring and treatment within a clinical setting that a patient would receive regardless of involvement in a research clinical trial.[28] Routine care in children with cancer includes outpatient and inpatient care as well as diagnostic and monitoring tests (e.g., serial MRIs). The majority of states in the US have laws or special agreements that require payment for routine care costs that occur within the context of participation in a research clinical trial.[28] As a result, standard medical care of children with cancer who are enrolled on randomized phase II and phase III clinical research trials is billed to insurance. Remarkably, however, a survey of COG affiliated psychologists revealed that the majority (75%) do not bill for routine neuropsychological assessments with clinical interpretation that occur within the context of participation in a clinical trial. We propose that there is sufficient scientific evidence to suggest that consistent neuropsychological assessment (monitoring) is an essential element of standard care that provides early evidence of adverse neurobiological events that increase the risk of functional impairment and disability or disease recurrence.[29,30,31,32,33] Just as other neurodiagnostic tests are billed when a child is receiving treatment on a research trial, or when a child receives care off study, costs for routine neuropsychological monitoring should always be billed.

When providing routine clinical neuropsychological monitoring, we encourage clinicians to utilize the health and behavior assessment codes to document the service under the child's cancer diagnosis and/or the late effects associated with neurotoxic effects of treatments. Unfortunately, insurance companies across the 50 states and District of Columbia vary widely in the degree to which they recognize these codes. According to the American Psychological Association, the health and behavior codes were developed to help psychologists accurately portray services they provide that focus not on mental health disorders but on the biopsychosocial factors affecting physical health.[34] Examples of issues that psychologists might address using these codes include not only neuropsychological monitoring but also medical adherence, management of treatment-related side effects, parental distress at diagnosis or relapse, or health-related risk behaviors. These billing codes also fit within the WHO's ICF and emphasize a biopsychosocial model of care.[11]

## Advantages of Brief, Repeated, Neuropsychological Monitoring

While administration of repeated comprehensive neuropsychological assessment batteries may be ideal, this practice may not always be feasible. This type of comprehensive evaluation is extremely time-consuming for the psychologist as well as the patient and family. One alternative strategy is the utilization of brief, repeated assessments to monitor neuropsychological functioning over time. These brief assessments can be tailored to target the areas of greatest sensitivity to neuropsychological decline (e.g., processing speed, working memory) and have a number of potential advantages.[27,35] A routine monitoring approach using an abbreviated assessment battery selectively utilizes limited temporal, personnel, and financial resources and is less burdensome on the child and family, while ensuring appropriate and essential monitoring of neuropsychological growth and development. Of course, when significant functional or medical events occur, or if monitoring results demonstrate significant declines, a more extensive, traditional, neuropsychological assessment can be completed. The lower costs of repeated brief

assessments emancipate resources, which can broaden access to neuropsychological care for children with cancer, potentially reducing health care disparities. Repeated monitoring allows the psychologist to identify disruptions in development and cognitive effects of treatment expeditiously. Additionally, this approach supports providing rapid written results to the treating physician(s) to guide additional biomedical treatment and monitoring, and to families who can make the assessment results available to the child's school. Just as functional assessments are the most sensitive indicator of recovery for individuals with concussion, repeat neuropsychological evaluation/monitoring with pediatric cancer patients with CNS-associated disease and/or treatment represents a similarly sensitive metric.[23] For third-party payers, our recommendations represent a cost-effective approach to the monitoring of CNS development and functioning as has been recommended by the FDA. There is evidence that this approach is cost-effective in other pediatric diseases and will facilitate initiation of interventions that can reduce disability.[36,37] The results of monitoring provides systematic, longitudinal research data that can lead to enhanced knowledge about the trajectory of neuropsychological functioning of children with cancers or treatment affecting the CNS, informing evidence-based practice.

## Challenges of Brief, Repeated, Neuropsychological Monitoring

There are potential diagnostic, resource (e.g., personnel, financial), and ethical challenges to consider related to this proposed model of brief, repeated evaluations. Diagnostically, if more extensive neuropsychological evaluation is deemed necessary based on results of the screening assessment, consideration must be given to burden on children and their families, with a focus on balancing the temporal demands with the collection of essential data. One example of a successful monitoring approach that has been carried out within COG is the ALTE07C1 protocol.[27] Within this protocol, children on several clinical trials are evaluated with an abbreviated assessment battery at three separate time points over a five year period. These are broad parameters but serve as one possible approach to monitoring neuropsychological functioning, providing clinically useful information, and balancing family burden. While there is a risk of under-recognition of subtle emerging changes in neuropsychological status when using a monitoring assessment approach, this risk is far less problematic than the complete lack of recognition associated with not examining the child, or doing so at only one time point. When adhering to this standard of care, we encourage flexible and individualized evaluations, as the monitoring assessment can be expanded when clinically indicated for any given child. It remains imperative that the psychologist retain clinical decision-making within this model.

Limitations in the availability of psychologists/neuropsychologists who are knowledgeable about and experienced with pediatric cancers and treatment affecting the CNS can also be a limitation in this model. Institutions with larger, more integrated pediatric oncology centers are more likely to have psychologists/neuropsychologists associated with the program who are knowledgeable and available to carry out this service. However, smaller centers may not have regular access to a psychologist, limiting how easily they could implement a neuropsychological monitoring approach to care. Utilization of resources within the Children's Oncology Group to supervise neuropsychological monitoring at distal, local sites, is one potential option.

Regarding billing challenges, the potential response from US insurance carriers may vary when results of the monitoring assessment suggest the need for a more comprehensive evaluation. Possible responses include: (1) data generated from the monitoring assessment is used to effectively demonstrate the medical necessity of more thorough medical and neuropsychological evaluation; (2) insurance companies deny additional, more extensive assessment, considering monitoring to be sufficient; or (3) insurance companies refuse payment for the monitoring assessment if no deficits are discovered. The latter scenario is most likely in states where health and behavior codes are not recognized or reimbursed. It is possible, however, that insurance companies will appreciate a more targeted approach. Based on the dynamic nature of pediatric cancer treatments on a child's CNS, prudent care strongly suggests that scheduled neuropsychological monitoring is in the best interests of the child and should be universally covered for this population of children with cancers affecting the CNS in order to reduce the risks for disability. In fact, in other countries, family financial health care burdens vary considerably, according to results from the Commonwealth Fund.[38] Many countries have no deductible for care and cap out of pocket expenses for families. For example, in Germany everyone must belong to one of the non-profit insurance collectives, thus there is no billing directly to a family when care is provided to children. In contrast, China has a limited multi-layered public health insurance system, thus there is considerable variability within settings where pediatric medical care is provided, frequently requiring families to pay for a substantial component of a child's care through individual medical savings accounts or out of pocket. With the interest in providing high quality care to children with cancer in the US, we need to be able to inform care with clinical research. As such, billing for neuropsychological monitoring and assessment services that contain a research component is necessary, feasible, and ethical.

This approach to care is not free of ethical challenges. Practically speaking, there are important considerations in cases in which the insurance company has denied authorization for payment of any neurobiological or neuropsychological assessment. Within the context of more traditional clinical care (not research), the family would be responsible for payment for the evaluation. The principle of justice emerges as particularly important in managing this challenge for children receiving care on a randomized phase II or III trial. If in the case of insurance denial one chooses to waive the fees to that family, this may be a violation of the principle of justice, as there would be a treatment disparity based on financial factors. When the measures are administered within a phase II or III clinical research protocol, it would be unethical to deny subject participation because of the absence of insurance coverage. Further, when neuropsychological testing is essential to the care of children with cancer, then it would seem important that such care be mandated for all children as part of the child's medical coverage for their cancer and covered using health and behavior codes, regardless of whether the child is treated on or off study. As the line between research and clinical care blurs in pediatric oncology, it may be the insurers who determine, at least in the short term, if and when such essential services are reimbursed for a particular child.

## Discussion

Contemporary therapies for pediatric cancers involving the CNS have resulted in a growing number of long-term survivors - many at risk for neuropsychological sequelae and disability

associated with their disease and the necessary life-saving treatments. Serial assessments to monitor neuropsychological development and functioning should be an essential component of care for patients with CNS-involved disease to facilitate early detection of emerging, adverse, neurobiological events and to dynamically inform medical care. These procedures allow an increased focus on learning, adaptive functioning, quality of life, moderating disability risk, and earliest detection of disease recurrence. Neuropsychological assessment is recognized as a sensitive neurodiagnostic procedure that contributes to medical and scientific decision-making and appropriate care of survivors with CNS-involved disease or treatments. The monitoring model utilizing a brief screening battery with psychometrically robust tools provides a cost-effective, efficient aspect of routine neuropsychological care, when followed, where indicated, by appropriate full-battery, neuropsychological testing. Adherence to such a standard should increase the proportion of patients who are provided essential neuropsychological care and, as a result, potentially benefit from early detection of declining neuropsychological functioning or other adverse events. This process should also reduce important barriers to developing appropriate plans of care for the cognitive rehabilitation of children found to be demonstrating critical levels of impairment. Neuropsychology will continue to play a key role in informing care and reducing disability for survivors of CNS cancers and cancers that require CNS-targeted therapies. The reimbursement for routine services is legally supported in most US states, when children are treated on or off phase II or III studies.

Early experience applying the neuropsychological monitoring model within COG has demonstrated that this approach to neuropsychological care is feasible.[27] Unfortunately, the majority of COG psychologists have not attempted to bill third-party payers for these services. Despite initial success and demonstrated feasibility of this model, the anticipated lack of reimbursement for these monitoring assessments significantly impacts study participation and essential elements of care. As a result, fewer children benefit from attempts at early detection of neuropsychological impairments and possible remediation, and fewer data are collected at the cooperative group level to help inform the development of future clinical trials. We hope this review will stimulate discussion of standard of care practices and ultimately influence future practice. Submitting for reimbursement of and payment for neuropsychological services should be the rule and not the exception, as our physician colleagues do for medical monitoring of survivors, regardless of research participation.

## Abbreviations Key

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| **COG** | Children’s Oncology Group |
| **CNS** | Central Nervous System |
| **MRI** | Magnetic Resonance Imaging |
| **EEG** | Electroencephalograph |
| **WHO** | World Health Organization |
| **ICF** | International Classification of Function, Disability & Health |

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|---|---|
| **FDA** | Federal Drug Administration |
| **CRT** | Cranial Radiation |
| **TBI** | Traumatic Brain Injury |
| **CPT** | Current Procedural Terminology |

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