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Monitoring Neurocognitive Functioning After Pediatric Cellular Therapy or Hematopoietic Cell Transplant: Guidelines From the COG Neurocognition in Cellular Therapies Task Force

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SUPPLEMENTARY MATERIALS

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The past decade has ushered in new therapies to treat pediatric cancer. Innovative cellular and immunotherapies (e.g., chimeric antigen receptor T-cells (CAR-T), bispecific antibodies, and immune checkpoint inhibitors [ICIs]) have shown success in clinical trials for a variety of cancer types. For pediatric patients with hematologic malignancies, these therapies offer potential fewer toxicities as compared to chemotherapy, irradiation, or hematopoietic cell transplantation (HCT). One notable success has been the use of CAR-T to target CD19⁺ B-cell acute lymphoblastic leukemia (ALL) [1], leading to Food and Drug Administration approval of tisagenlecleucel in 2017. HCT remains a mainstay of treatment for over 2000 pediatric patients each year, with more pediatric patients receiving HCTs over time [2,3]. Whereas acute neurologic complications after HCT are typically due to medication or infectious causes, CD19⁺-targeted CAR-T is associated with acute immune-mediated neurotoxicity. Research regarding the long-term neurocognitive outcomes for pediatric patients receiving cellular therapies (CT) or HCT is notably sparse. With numerous cellular and immunotherapies in development to treat different cancer types, systematic comparisons of these therapies and associated short- and long-term toxicities is needed to counsel patients and their families and develop appropriate models of multidisciplinary follow-up care.

Neurocognition can be defined as cognitive processes related to specific neural mechanisms occurring in the brain [4]. Estimates of the rate of neurocognitive late effects vary, with some studies suggesting that over half of childhood cancer survivors develop cognitive impairments [[5]. Children with central nervous system (CNS) tumors and ALL have been identified with the greatest risk for cognitive late effects, although a broader range of diagnostic groups also carry risk for cognitive impairments. Existing research has been limited by the complexity of defining neurocognitive late effects, as well as the lack of baseline (pre-cancer) cognitive data for most children. Many studies assess potential cognitive deficits using population-based norms alone, thereby missing intraindividual changes and more subtle deficits that may not be detected on common measures of cognitive functioning. Potential deficits for children with hematologic malignancies include difficulties with concentration, working memory, executive function, processing speed, language, motor function and academic achievement [5]. Children with CNS tumors may have additional deficits related to the tumor, treatment, or potential complications, including decline in intellectual quotient (IQ) scores secondary to cranial radiation therapy. Cognitive deficits can have widespread impact on educational and vocational achievements, overall health, and quality of life [6].

Many unknowns remain within the domain of neurocognition in cellular therapy. Additional clarity is needed to identify patients at high risk for cognitive impairment, determine method and timing of monitoring for cognitive late effects, and clarify neurocognitive endpoints of interest. To this end, the Children's Oncology Group (COG) Neurocognition in Cellular Therapies Task Force, a joint effort of the Behavioral Science and Cellular Therapy Committees, was created to develop evidence-based guidelines for studying neurocognitive outcomes in patients undergoing pediatric CT, immunotherapies, or HCT. These guidelines serve to guide clinicians in their efforts to counsel patients and families (before and after

treatment) and researchers as they develop formal methods of studying neurocognitive outcomes within this patient population.

RISK FACTORS FOR DEVELOPMENT OF NEUROCOGNITIVE LATE EFFECTS

Most of what is known about neurocognitive outcomes after CT, immunotherapies, or HCT is extrapolated from the larger pediatric cancer literature. Potential risk factors can be broadly conceptualized as *potential neurotoxicity incurred through treatment (direct or indirect) and factors intrinsic to the patient and their environment* (Table 1).

Direct Mediators of Neurotoxicity

Chemotherapy—Children treated using contemporary ALL protocols involving intrathecal chemotherapy are at risk of lower performance IQ compared to their siblings and healthy controls. Specifically, methotrexate (high-dose or intrathecal) and dexamethasone included in treatment protocols have been correlated with deficits in working memory and executive functioning in a dose dependent manner in some studies [7–9], although methotrexate dosing or steroid type was unrelated to processing speed and IQ in children with B-lineage ALL enrolled on COG AALL06N1 [10]. Higher cumulative methotrexate intrathecal dosing has been associated with elevated CSF biomarkers and the presence of leukoencephalopathy on neuroimaging [11]. Leukoencephalopathy is identified in approximately 25% in children with ALL and is coupled with an increased risk of neurocognitive deficits [12]; onset of leukoencephalopathy appears related to observed learning, memory and attention difficulties. Cognitive deficits have also been noted in children with CNS tumors treated with radiation-sparing chemotherapy, although these studies are complicated by tumor-related factors [5]. Although much of the literature on neurocognitive late effects has focused on ALL or CNS tumors due to the associated higher risks, cognitive deficits have been described for other cancer types. For example, children and adolescents with acute myeloid leukemia (AML) treated with chemotherapy alone were more likely to experience neurocognitive deficits compared to healthy controls, highlighting the impact of CNS-directed chemotherapy agents in other diagnoses [13].

Studies focused on pediatric HCT recipients report cognitive deficits in 20% to 40% of HCT survivors [13–22]. However, it has been difficult to tease out the relative contribution of prior chemotherapy (or other treatments) and HCT. Within disease-specific studies, there are conflicting results when comparing neurocognitive outcomes in children treated with HCT versus chemotherapy alone [13,23]. Studies including baseline testing before HCT have found average IQ scores and specific cognitive deficits in attention, processing speed, and memory [15,17,19,24,25]. The first year after HCT appears to be a critical timeframe for developing neurocognitive deficits, with some children showing improvement or stabilization in cognition beyond 1 year [18,21]. For those with persistent deficits, progressive declines have also been observed over time [17]. Because most children receive myeloablative conditioning with or without total body irradiation (TBI; discussed below), it is unclear whether less toxic regimens would lessen the potential for cognitive late effects. Overall, the existing literature suggests that neurocognitive deficits often present by the first

year after HCT, although deficits can emerge later with a variable course, indicating the need for long-term monitoring.

Research regarding CAR-T is less robust. Current lymphodepleting regimens for CD19-specific CAR-T products rely on a backbone of fludarabine, cyclophosphamide, or both [26]. Case studies have linked fludarabine to a rare, devastating neurotoxicity at higher doses and, as such, it was implicated as a possible cause of fatal cerebral edema observed in six participants enrolled on initial CAR-T studies [27]. This was later disproved and continues to be used in lymphodepleting regimens.

Radiation—CNS radiation has been shown to increase the risk of neurocognitive impairment in a dose-dependent manner, with progression of deficits over time [5]. It remains unclear whether TBI-containing regimens (e.g., delivering a lower overall dose to the CNS) impart any increased risk of neurocognitive deficits. Some studies have indicated a deleterious effect of TBI on cognition, especially in younger children [16–18,23], whereas only small or inconsistent effects of TBI have been noted in other studies [25,28,29]. CNS radiation can also lead to radiation-induced arteriopathy, which is a known risk factor for stroke (and thus further cognitive changes) [30]. Thus TBI-containing regimens may contribute to neurotoxicity in these children. Of note, TBI has not been routinely used in lymphodepleting regimens for CAR-T.

IMMUNE- OR CELLULAR-MEDIATED NEUROTOXICITY AFTER HCT AND CT

Graft versus host disease (GVHD) can be a severe and debilitating complication after HCT. Children who develop GVHD are more likely to develop neurocognitive deficits [15,17,28]. GVHD can affect the peripheral nervous system (e.g., myositis, immune neuropathies, or myasthenia gravis) and can rarely affect the CNS [31–33]. A recent review identified 46 cases of chronic CNS GVHD in the literature, presenting most frequently with seizure, cranial neuropathy, cognitive dysfunction, or stroke-like episodes [34]. Brain magnetic resonance imaging results were abnormal in nearly all cases; asymmetric white matter lesions were observed in most, although hemorrhagic or ischemic changes were seen in a subset. Histology most frequently showed a lymphocytic vasculitis followed by microglial involvement [34–36]. Antibodies and immune biomarkers have been detected in a subset of patients [37–39]. Most responded to immunosuppressive treatment. It is unclear whether neurocognitive deficits identified after allogeneic HCT could be a manifestation of chronic GVHD in certain patients. If so, this is an underrecognized complication of HCT deserving of additional investigation.

Immune effector cell-associated neurotoxicity syndrome (ICANS) is a well-described complication of CAR-T therapy. An analogous neurotoxicity can occur with the bispecific antibody blinatumomab [40]. While the incidence and severity vary with different targets and constructs [40,41], ICANS is characterized by altered levels of consciousness, cognitive impairment, aphasia, motor weakness, seizures, and, in its most severe form, cerebral edema. Deterioration in handwriting is an early predictor of ICANS for adults and is routinely tracked in the initial weeks after CAR-T infusion [42,43]. The role of neuroimaging remains unclear, since imaging may be normal even in severe ICANS [44]. Developing higher-grade

cytokine release syndrome (CRS) increases the risk of ICANS, but serum cytokine panels differed in pediatric patients with ICANS with CRS versus those without, suggesting different processes [45]. Growing evidence suggests that the underlying mechanism in ICANS involves endothelial dysfunction in the setting of a proinflammatory response [46,47]. Similarly, T-cell adhesion to endothelial cells has been implicated in blinatumomab neurotoxicity. Possible factors involved in the development of ICANS include higher disease burden, peak CAR Tcell expansion, and proinflammatory cytokines [44]. Higher blinatumomab dosing was associated with the incidence but not severity of neurotoxicity in 1 adult study [48], whereas no dose response was reported in another [49]. Symptoms typically resolve after ICANS or blinatumomab-related neurotoxicity, although chronic sequelae can occur. The use of CD19-directed CAR-T and blinatumomab have been increasing; thus whereas further studies to better understand the mechanism of ICANS and identify potential treatments are needed, this should be paired with ongoing cognitive monitoring in patients who have received these treatments. In addition, it is likely that different toxicity profiles will emerge as the field expands beyond using T-cell platforms targeting B cells.

ICIs are a relatively new class of drugs that target cancer by enhancing antitumor immune responses. They have shown effectiveness against a broad range of tumor types [50,51] and are increasingly being used in pediatric studies [52,53]. ICIs are commonly paired with other cancer treatments [51]. Autoimmunity is a well-described complication in adults [50]. Although uncommon, ICI-related neurologic autoimmunity can occur at any time (most often within the first 3 months), with variable presentation [50,54,55]. Treatment includes holding or discontinuing the ICI and different immunosuppressive treatments (e.g., steroids, Intravenous Immunoglobulin (IVIG)) have been explored. Improvements have been seen in adults, but little is known about the incidence or the course in children [30,55].

Disease-Mediated Neurotoxicity

Children with CNS tumors are at risk of disease-mediated damage, although this is generally localized. The presence of leukemic cells in the CNS carries inherent risks of neurotoxicity without overt CNS disease. Newly diagnosed patients with ALL without measurable CNS disease have been noted to have elevated CSF biomarkers of neuroinflammation and myelin destruction [56]. To date, the experience using CD19-specific CAR-T cell therapy for CNS disease (isolated or in combination with marrow disease) has been limited, in part because of exclusion from pivotal clinical trials because of concern for increased toxicity [1,57,58]. Recent single- and multi-institutional studies have not observed increased neurotoxicity in pediatric patients with CNS disease after infusion with tisagen-lecleucel [59–61].

Other Direct Mediators of Neurotoxicity

Medications commonly used to prevent or treat GVHD can affect neurocognition. The ongoing immunosuppression needed to prevent or treat GVHD increases the risk of viral infections, which in turn, can lead to neurocognitive impairments effecting memory, speed, or attention [62–64]. Corticosteroids are well known to directly affect cognition and memory [65]. Calcineurin inhibitors can be neurotoxic and has been linked to transplant-associated thrombotic microangiopathy (TMA) and posterior reversible encephalopathy syndrome.

Often thought of as reversible processes, recurrence or long-term sequelae occur in 10% of children [66–68]. Children who develop seizures during cancer treatment carried increased risk for deficits in attention, working memory, processing speed, and intelligence, with findings of leukoencephalopathy on magnetic resonance imaging [69]. Sepsis, although not bacteremia, was related to impairments in spatial planning, visuospatial working memory, verbal fluency, attention, and vigilance in pediatric ALL survivors [70].

Indirect Mediators of Neurocognitive Dysfunction

Neurocognition can also be indirectly impacted by certain factors. Prolonged hospitalizations, time away from school/work, and social isolation have all been associated with short-and long-term cognitive deficits [71,72]. Depression and anxiety are known to negatively impact certain neurocognitive domains. Data is conflicting whether pediatric survivors are at higher risk of depression, anxiety or posttraumatic stress disorder, although posttraumatic stress symptoms are common [73,74]. A recent study from the Childhood Cancer Survivor Study identified a positive role of exercise in adult survivors of childhood cancer. Rates of self-reported depression, anxiety, and cognitive impairment (task completion, organization, and working memory) were inversely related to the amount of exercise (hours/week) reported by the survivors [75]. Poor sleep and fatigue affect many pediatric HCT survivors [76], with female survivors appearing to be more susceptible to these effects [77]. Higher anesthesia exposures (cumulative and longer duration) have been associated with slower processing speed in pediatric cancer survivors [78]. Neurosensory deficits (e.g., hearing impairment) secondary to certain chemotherapy agents have been identified as a risk factor for neurocognitive impairments in pediatric cancer survivors [79].

Patient-related or environmental risk factors

It is generally accepted that younger age at the time of treatment is associated with an increased risk for the development of neurocognitive deficits after chemotherapy for ALL or brain tumors, irrespective of whether CNS-directed radiation is given [80–83]. Results from studies focused on HCT recipients are less straightforward [15,16,25,29,63,84–86]. Female survivors developed attention issues more frequently after chemotherapy or HCT in several studies, whereas males and females had different patterns of deficits in other studies [85,87–92]. Certain chronic diseases can increase a child's risk (e.g., sickle cell disease, severe combined immunodeficiencies) or directly cause neurocognitive deficits (e.g., inborn errors of metabolism) unrelated to subsequent therapies [62,93–95]. Genetic polymorphisms linked to certain metabolic pathways have been associated with neurocognitive impairments in survivors of pediatric ALL, indicating an underlying predisposition to toxicity in some children [96,97].

Several longitudinal studies demonstrated that pre-HCT neurocognitive testing results was the strongest predictor of post-HCT status and was related to the child's socioeconomic status (SES) [18,86]. These studies highlight the importance of including a broader assessment of family psychosocial risk before HCT (e.g., Psychosocial Assessment Tool) [98] and recognizing the impact of SES on cognition and access to resources.

Patient-reported outcomes

Cognitive, memory and attention issues are commonly self-reported by HCT survivors. Although long-term neurocognitive outcomes of CAR-T remain unknown, several studies have included patient-reported outcomes in adults [99]. Memory, attention and concentration issues were self-reported by 40% of adult patients 12 to 18 months after CAR-T [100]. Self-reported cognitive dysfunction in adults correlated strongly with poor global mental and physical health scores, pain interference, sleep disturbance, fatigue, depression, and anxiety. This study also highlights the potential difficulties in assessing neurocognitive outcomes in the population of individuals undergoing CT and HCT. Children enrolled on the ELIANA trial reported lower than average school functioning than population norms during the first year after CAR-T; only 20% reported age-appropriate functioning [101].

Literature Supporting Recommendations

A systematic review was initiated to examine the existing literature regarding neurocognitive outcomes in pediatric HCT and CT patients. An electronic search of the literature was conducted in MEDLINE (PubMed), EMBASE (Elsevier), and Web of Science (Clarivate Analytics) from inception to July 17, 2020, with no restriction in start date. An updated search was conducted on July 18, 2021, to retrieve articles published since the initial search. Both searches were conducted by professional medical librarians (K.B. and B.M., respectively) using the same search strategy, which included a combination of controlled vocabulary and keywords representing neoplasms, immunotherapies, and focusing on the pediatric population (Supplemental Table S1). Search results were not limited by language, and editorials, comments, preprints, notes, and conference abstracts were excluded from Medline and Embase based on the database format. Animal-only studies were excluded from Medline. In Web of Science, results were limited to the document types—article, review, letter, or proceedings paper. This systematic review was done in close accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (Figure 1). Titles and abstracts retrieved from the search were screened independently by 6 reviewers using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). Conflicts were resolved by an independent reviewer. Full-text articles were retrieved if the abstract provided insufficient information to establish eligibility or if the article passed the first eligibility screening. The medical research librarians did not participate in the screening, full-text review, or data abstraction. Screened abstracts included oncology studies in humans that described neurologic or neurocognitive adverse effects or toxicities. Using the defined inclusion criteria (CAR-T or HCT, pediatric, neurologic or neurocognitive, long-term adverse or late effects), we identified 14 relevant articles regarding neurocognitive outcomes of HCT. Articles describing the same cohort and were considered together. Articles that used only parent- or patient-reports were excluded. One relevant article for CAR-T was identified and, despite the early post-infusion timeframe, warrants mentioning. These studies were then assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework [102–105]. All studies were observational, were a mix of prospective and retrospective, and met GRADE criteria for moderate or low-quality studies. An overview of the articles is presented in Table 2.

Based on the review of available literature and insight gathered from the authors of this publication, the following recommendations are offered for clinicians. Guidelines for researchers are presented below.

Recommendations for Clinicians

Recommendation 1: It is important to acknowledge that timely access to neurocognitive evaluations may vary among centers and may be hindered by insurance coverage or other factors necessitating *a triage process to best allocate resources*. When identifying patients in greatest need for neurocognitive assessment, clinicians should identify those with treatment histories carrying specific risk for cognitive late effects. Individuals with an elevated risk for cognitive late effects of treatment include those with prior CNS pathology, prior CNS-directed radiation therapy or TBI, and those with a history of HCT (with or without GVHD).

1. Special attention should be paid to patients who experience CRS or ICANS, until it is clear whether CRS or ICANS contributes to later neurocognitive deficits
2. Age of the child at treatment is a key risk factor. Children 6 years and younger at the time of treatment have been identified as having notable risk for cognitive late effects.

Recommendation 2: When completed, neurocognitive testing should focus on specific cognitive domains potentially at-risk secondary to HCT, CAR T-cell therapy, and other immunotherapies (Table 3).

1. Commonly affected cognitive domains include attention and working memory, executive functioning, processing speed, language, motor coordination, and academic achievement. These cognitive areas can affect adaptive functioning and vocational performance. Survivors may benefit from targeted strategies (e.g., educational accommodations, job training programs) in these cognitive domains.
2. Patient age should be used to guide selection of measures. Certain cognitive domains (e.g., executive functions) will not become functionally salient or evaluable until later in childhood.
3. When estimating cumulative risk for cognitive deficits, clinicians should consider prior treatments and potential impact over time.

Recommendation 3: Selected neurocognitive measures should be able to be administered at key time points that are salient for HCT, CAR-T cell therapy, and other immunotherapies.

1. The nature of these treatments indicates that a pretreatment assessment may be important. This may include relying on parent report of cognition if patients are unable to participate in direct testing prior to undergoing HCT or CAR-T cell therapy. Possible proxy measures include the Behavior Rating Inventory of Executive Function (BRIEF) [106] or the NIH PROMIS Cognition scale (<http://www.healthmeasures.net>).
2. In the initial months after CT, a standardized measure to assess neurotoxicity symptoms should be used [107].

3. The recommended time points for assessment include before HCT/CT, 1 year, 2 years, and 4/5 years after HCT/CT. Additional follow-up assessments are recommended to monitor emerging higher-order cognitive functioning deficits over time, but optimal timing and frequency of these assessments remains unclear.
4. For CT patients, an earlier time point is needed to capture possible acute neurocognitive changes within the first year after infusion.

Recommendation 4: Because patients receiving these types of treatments may struggle with fatigue at varying times during and after treatment, a briefer cognitive battery may be necessary. Clinicians should identify specific subtests within broader assessment tools that gather meaningful cognitive data that is relevant given the patient's treatment history and the presenting issue.

1. Efforts should be made to identify measures that can be administered across the life span or have well-established developmental correlations (e.g., Wechsler versions of intellectual batteries for preschool, childhood, and adulthood ages).
2. If possible, clinicians should select cognitive measures that have alternate forms for repeat assessment over time.
3. To examine neurocognitive functioning of HCT patients:
 - a. It is recommended that *attention and working memory*, *processing speed*, and *executive functioning* domains should be assessed. Inclusion of a brief intellectual estimate is recommended unless TBI/CSI was received.
 - b. Given the impact of HCT on school attendance and participation, study teams are encouraged to consider including measures of academic achievement to track possible impact on academic achievement over time.
4. To examine neurocognitive impact of CAR T-cell therapy:
 - a. Cognitive batteries should include measures of attention and working memory, processing speed, language, and executive functioning.
 - b. Because CT is typically delivered on an outpatient basis, less disruption would be expected to the patient's school attendance and schedule. It is important to consider the impact of other salient cognitive domains on academic achievement and progress (e.g., attention, memory, executive functioning). A brief academic screen may be appropriate to include in pre-infusion assessments, as well as subsequent follow-up visits.

Guidelines for Researchers

The following guidelines are provided for researchers designing studies on pediatric patients receiving CT and HCT. These guidelines are based on a review of the evidence and expert opinion, but potential areas for research remain (Table 3).

Guideline 1: Within the identified diagnostic or treatment population, researchers should *define specific subgroups with elevated risk for cognitive effects of treatment*. This should include individuals with prior CNS pathology, prior CNS-directed radiation therapy or TBI, and those with a history of HCT (with or without GVHD).

1. Investigators should collect accurate dosing and timing of prior CNS-directed treatment.
2. Special attention should be paid to patients who experience CRS and/or ICANS. It is unknown whether CRS or ICANS contributes to later neurocognitive deficits. Investigators are encouraged to consider this in their study design.
3. There are several areas, such as the impact of prior dexamethasone or methotrexate exposure, which would benefit from careful investigation in future trials. Until such time, efforts to address possible confounding effects should be incorporated into statistical plans.

Guideline 2: Researchers should *delineate specific cognitive domains potentially at-risk* secondary to HCT, CAR T-cell therapy, and other immunotherapies. Past research has implicated such deficits as decline in intellectual functioning, attention and working memory weaknesses, executive dysfunction, slow processing speed, language impairment, motor functioning difficulties (accuracy, speed), and lower academic achievement.

1. Investigators are encouraged to consider the impact of age and prior treatment when identifying key cognitive risk domains.
 - a. Changes in intellectual function are less likely after chemotherapy-based preparative regimens, suggesting that less time should be designated for intellectual assessment in these patients.
 - b. Certain cognitive domains (e.g., executive functioning) will not emerge or become salient until later in childhood; Batteries should make accommodations for measures related to mature cognitive functions.
2. When studying novel therapies, investigators are encouraged to reference existing literature for therapies with similar pathophysiological pathways when determining cognitive domains at risk.
3. Investigators should define neurocognitive dysfunction based on the specified study tools. Specifically, it is important to state whether neurocognitive dysfunction will be defined based on normative ranges (e.g., scores less than 1.0 SD below the mean) or differences in participants' scores on serial assessments. This decision should be made based on the hypothesis and suspected mechanism for cognitive change.

Guideline 3: Identified tools must meet requirements for administration at *key time points* that are salient for BMT, CAR-T cell therapy, and other immunotherapies.

1. Although many research-based neurocognitive batteries use short- and long-term time points after initiation of treatment, the nature of CT indicates that a

pretreatment time point of assessment may be of importance. This may include relying on parent report of cognition if patients are unable to participate in direct testing before undergoing HCT or CAR-T cell therapy.

2. Investigators are encouraged to consider the sensitivity of the identified assessment methods in *capturing key cognitive changes* that may predict future cognitive difficulties (e.g., acute aphasia, delirium). Researchers should consider inclusion of a standardized measure to assess neurotoxicity symptoms.
3. The recommended time points for HCT include before HCT, 1 year, 2 year, and 4 or 5 years after HCT. Additional longer-term follow-up dates are strongly recommended, because they will allow for examination of emerging higher-order cognitive functioning deficits over time.
4. Similar time points are encouraged for studies of CT patients, adding an earlier time point to capture possible acute neurocognitive changes.
5. Investigators should consider aligning time points for patients receiving HCT and CT when designing studies in which both are permitted.
6. Efforts should be made to align cognitive follow-ups with routine follow-ups or other study visits to increase enrollment and decrease time demands on patients and families.

Guideline 4: Investigators should consider *logistical and demographic factors* when selecting assessment tools. Currently, the COG is comprised of over 200 U.S. and Canadian centers, and as such, many oncology patients need to travel for their treatment. Adding to this issue, only a subset of centers provides HCT and fewer are approved to provide tisagenlecleucel. This leads to care divided between the HCT/CT center (treatment and initial follow-up) and the “home” hospital (long-term monitoring). Although understandable, it does complicate study design and planning for neurocognitive assessments, as different hospitals may have varying availability of psychologists or neuropsychologists to complete study assessments.

1. To address this, researchers may consider using measures *that can be administered remotely*. Computerized testing or online reporting forms can provide efficient evaluations and monitoring at multiple time points, particularly if testing is done within standardized settings such as a hospital clinic space. Completion of tele-neuropsychology requires careful consideration of the psychometric and ethical concerns with this manner of test administration [108].
2. If investigators choose to avoid tele-neuropsychology or remote computerized administration of measures, an alternative could include electronic administration of age-normed and gender-normed parent or self-rating scales. However, relying on parent- or self-ratings may not provide as sensitive data regarding neurocognitive outcomes as direct cognitive assessment.
3. Investigators should explore secure electronic methods for collecting data from rating scales, reducing the need for sites to be responsible for storing paper forms.

Guideline 5: Investigators are encouraged to *identify specific subtests within identified assessment tools that gather meaningful cognitive data*. Consideration should include potential risk factors for the study cohort of interest (e.g., impact of prior therapies, medical sequelae).

1. Because intellectual functioning may not be the primary domain affected in HCT, researchers are encouraged to use a brief assessment of intellectual functioning rather than a full intellectual battery. For example, use of a well-validated 2-subtest or 4-subtest intellectual estimate may be adequate.
2. All efforts should be made to identify measures that can be administered across the life span or have well-established developmental correlations (e.g., Wechsler versions of intellectual batteries for preschool, childhood, and adulthood ages). As previously mentioned, researchers are encouraged to consider assessment tools with flexible administration.
3. Future COG studies are encouraged to consider inclusion of well-validated computerized batteries such as Cogstate (<http://cogstate.com>) [109]. Cogstate has been used in therapeutic areas such as ALL, neurofibromatosis type 1, lymphoblastic lymphoma, medulloblastoma, and sickle cell disease. This battery includes measures of processing speed, attention, memory, executive function, and social emotional cognition, with a pediatric specific battery available for children as young as 4 years of age. For researchers outside of COG, they may consider an instrument such as the NIH Toolbox, a computerized battery of cognitive, motor, and psychosocial assessments designed to be used with children as young as 3 years [110]. Both batteries use age norms and can be administered across the lifespan, into adulthood. There is evidence to support test-retest reliability, sensitivity and specificity, and discriminative and predictive validity of both measures in pediatric cancer patients.
4. Neurocognitive batteries should be thoughtfully created in conjunction with a multidisciplinary team including neuropsychologists and other experts in cognitive assessment. This is particularly salient given the relative current paucity of information related to neurocognition in CT, as future study teams may have access to updated information that further clarifies the cognitive profile of these patients.
5. For studies examining neurocognitive functioning of HCT patients (Table 4):
 - a. Assessments should include *attention and working memory, processing speed, and executive functioning* measures. Inclusion of a brief intellectual estimate is recommended.
 - b. Given the impact of HCT on school attendance and participation, study teams are encouraged to consider including measures of academic achievement to track possible impact on academic achievement over time.
6. For studies examining neurocognitive impact of CAR T cell therapy (Table 4):

- a. Cognitive batteries should include measures of attention and working memory, processing speed, language, and executive functioning.
- b. As CT is typically delivered on an outpatient basis, less disruption would be expected to the patient's school attendance and schedule. Investigators should consider the impact of other salient cognitive domains on academic achievement and progress (e.g., attention, memory, executive functioning). A brief academic screen may be appropriate to include in preinfusion assessments and subsequent follow-up visits.

Future Directions

These guidelines were initially designed to aid investigators in their attempts to better understand neurocognitive outcomes of pediatric patients undergoing cellular therapy and HCT. Within these guidelines, there are several suggestions extended to clinicians involved in the neuropsychological care of patients receiving these treatments (e.g., appropriate timing and duration of evaluations, salient cognitive domains for HCT patients). Specifically, the guidelines may assist in choosing appropriate assessment measures and timepoints to monitor neurocognitive symptoms in clinical patients. Ongoing research is investigating cellular therapies with different targets, manufacturing (e.g., off-the-shelf), cellular type (e.g., natural killer cell), and indications (e.g., CNS tumors, neuroblastoma, sarcomas). We hope that these guidelines will facilitate the growth and development of this important knowledge base as the use of CT and HCT continue to expand.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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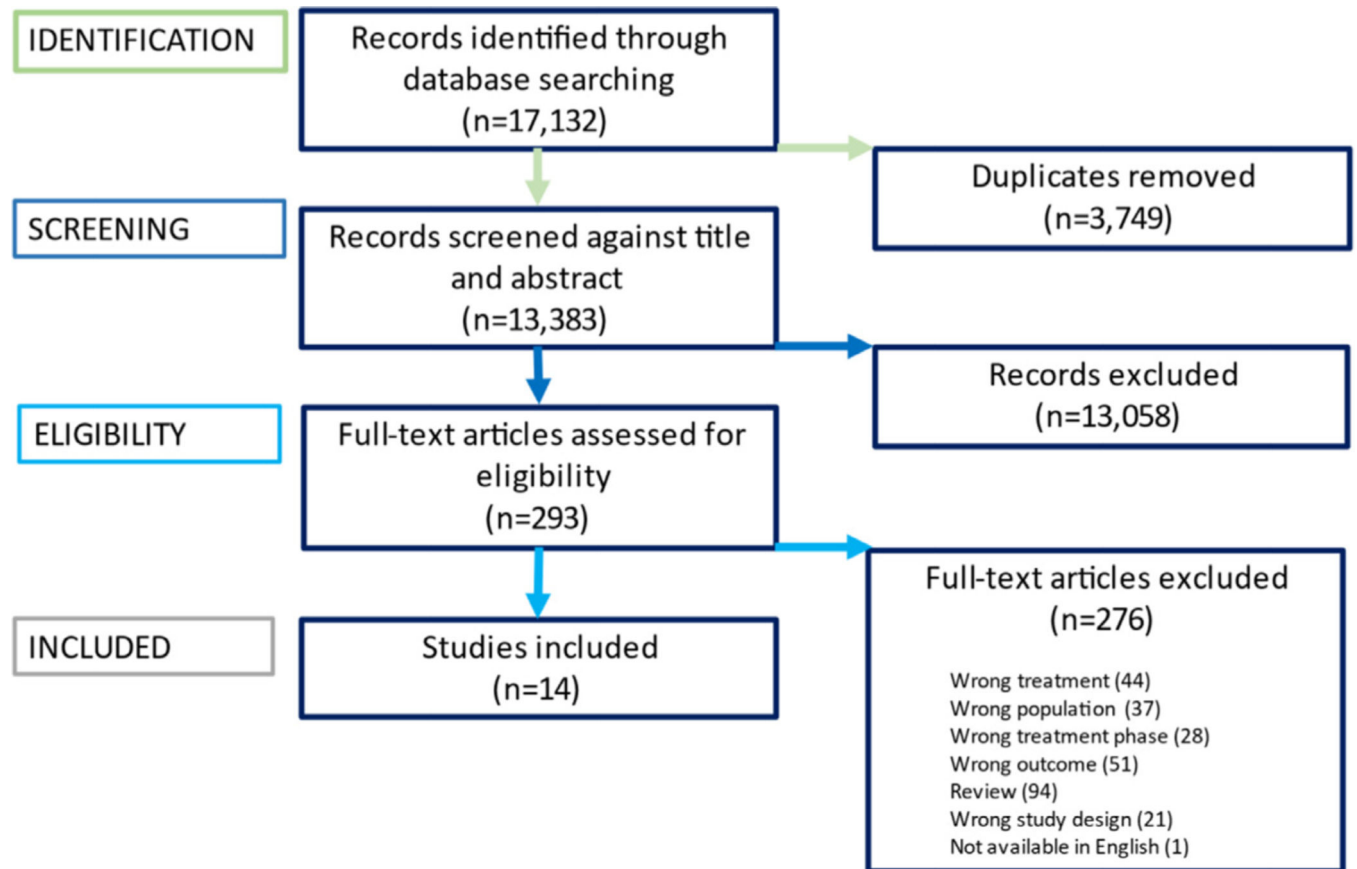


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram.

Table 1

Potential Mediators of Neurocognitive Outcomes After Hematopoietic Stem Cell Therapy, Cellular Therapy, or Both

Patient-Related or Baseline
Environmental factors: Socioeconomic status, healthcare accessibility and other social determinants of health
Baseline neurodevelopmental status: Baseline cognitive skills, pre-existing attention or learning issues
Genetic & metabolic mediators: Trisomy 21, Homocystinuria, genetic polymorphisms that are associated with attention or learning issues
Other host factors: Age, general health condition, other comorbidities
Direct Mediators
Before HCT or CT
Treatment related: Chemotherapy exposure considering route (Intra-theal or systemic), dose, type; Radiation therapy exposure considering type, dose, and field; Presence of polymorphisms known to increase risk of toxicities
Disease-related: Presence of CNS disease and degree of CNS involvement
Development of neurotoxicity: Stroke, infections, drug related
Other comorbidities: ICU stay, renal and liver functions, cardiopulmonary condition, other organ specific toxicities
HCT or CT-Related Exposures
Treatment related
Chemotherapy
Use of total body irradiation (TBI) or craniospinal irradiation (CSI)
Development of neurotoxicity
Drug related (Calcineurin inhibitors), infection related (viral, fungal, others), vascular insults
ICANS or CRS development
Other comorbidities: GVHD, TMA, ICU stay, renal and/or liver dysfunction, other organ specific toxicities
Indirect Mediators: Concurrent psychiatric conditions, fatigue or poor sleep, exercise, and other lifestyle factors. Concurrent medications that may impact attention, sleep, etc.

HCT, hematopoietic cell therapy; CT, cellular therapy; ICANS, Immune effector cell-associated neurotoxicity syndrome; CRS, cytokine release syndrome; ICU, intensive care unit; GVHD, graft-versus-host disease; TMA, transplant-associated microangiopathy.

Table 2

Pediatric HCT Studies With Neurocognitive Outcomes

Reference	Population	Study Design	Measures Used*	Testing Time Point	Findings
Kramer [21]	65 children with malignant, immunodeficiencies, or nonmalignant hematologic diseases; HCT between 1986–1994	Single center, prospective	Bayley, Stanford-Binet-IV, WISC-R, Vineland, WRAT-R, VMI	Pre-HCT; Post-HCT at 1 year, 3 years	Decline in IQ noted from baseline to 1 year but remained stable to 3 years; no impact of radiation, chemotherapy, age at HCT, sex
Simms [25]	47 children (birth–16 years old) with malignancies or aplastic anemia; HCT's before 1999;	Single center, prospective	Bayley, WPPSI, WISC-R, WISC-III	Pre-HCT; Post-HCT at 1 year, 2 years	Mean IQ at all timepoints within normal limits; preHCT scores lower in younger (<3 years at HCT) compared to older children; younger children's scores decreased at 2 years after HCT. Normal IQ in older children given TBI or chemotherapy regimens.
Perkins [14]	17 children (<3 years old) with AML or ALL; HCT between 1981–2000. Two thirds given TBI	Single center, cross sectional	VMI, Connors, CVLT or CVLT-C, WISC-R, WISC-III, Purdue Pegboard, TOVA, WAIS-II, ABAS	Time post-HCT: mean 11.6 years (range, 3.3–22.3 years)	IQ and academic achievement within normal limits. Specific learning difficulties noted, especially attention, short-term memory.
Lajiness-O'Neill [15]	30 children (>4 years old) at least 1 year after HCT; HCT between 1998–2011	Single center, retrospective	WISC-IV, WJ-III ACH, CVLT or CVLT-C, Connors, others	Time post-HCT: mean 5 years (range, 1–14 years)	Mean IQ in low average range (processing speed an area of weakness). Significant variability seen between individuals. No effect of age at HCT or TBI; time since HCT associated with increased attention difficulties, perceptual reasoning; acute GVHD severity inversely associated with memory function.
Smedler [16]	22 children (<4 years old) with malignant or nonmalignant diseases; HCT from 1992–2004	Single center, prospective	WISC-III, WPPSI-R, VMI, others	Time after HCT: mean 5 years (SD 3.5 years)	Those given busulfan performed at age level in verbal but below age in executive and visuospatial domains; those given TBI had pervasive impairments (motor deficits, varying levels of perceptual, executive, and cognitive).
Shah [17]	38 children (>42 months old) with leukemia or lymphoma between 1998–2004; healthy siblings	Single center, prospective	WISC-III, WPPSI-R, VMI, WRAT-III and others	Pre-HCT; post-HCT at 1, 3, and 5 years	Significant declines in patients given cranial radiation versus chemotherapy only. Memory continued to decline 5 years after HCT. Verbal deficits present at 5 years. Visual motor development decrease pre- to 1 year and then stabilized.
Willard [18]	183 children with malignant or nonmalignant (40%) diseases; 52% received TBI	Single center, prospective	Bayley, WPPSI, WISC-R, WISC, WAIS-R, WAIS-III	Pre-HCT; Post-HCT at 1, 3, and 5 years	Baseline IQ scores in normal range. SES associated with baseline scores; Age effects seen earlier (first year) and TBI effects seen after 1 year after HCT. Recovery faster for chemotherapy only; youngest given TBI with most deficits
Kupst [19]	153 children with malignant or nonmalignant diseases; HCT between 1988–1999; nearly all given TBI	Single center, prospective	Bayley, Vineland, WPPSI-R, WISC-R, WISC-III, WAIS-R, parent reports	Pre-HCT; post-HCT at 1 and 2 years	IQ stayed stable over time; strongest predictor was pre-HCT function; SES was correlated with IQ scores at all 3 timepoints; arithmetic was significantly lower before and after
Hiniker [20]	41 patients (4–21 years old) with ALL and CNS involvement; all given TBI and cranial radiation boost; HCT from 1986–2011	Single center, retrospective	WAIS-R, WISC-IV, WJ-III ACH, WRAML2, grooved pegboard test	Time post-HCT: range, 7.2–27.3 years	IQ stayed stable over time; relative deficiencies noted in processing speed, working memory

Reference	Population	Study Design	Measures Used*	Testing Time Point	Findings
Weintraub [110]	16 children with neuroblastoma at least 1 year from HCT; 8 given TBI	Single-center, cross-sectional	WISC-III, WRAML2, VMI, WIAT, others	Median time from diagnosis: 6 years (1.6–13 years)	No differences in TBI versus non-TBI; above-average scores in cohort
Barrera [29]	46 children (3–16 years); healthy siblings	Single-center, prospective	WISC-III, WRAT-III, VMI-IV	Median time from diagnosis: 19.9 months (SD 19.5)	Cognitive outcomes at 2 years after HCT were similar to siblings
Barrera [24]	83 children (3–17 years) with malignancies or hematologic disorders	Single-center, prospective	WPPSI-R, WAIS-R, VMI-IV, WRAT-III	Pre-HCT; post-HCT at 1 and 2 years	IQ remained within norms; older children had better scores in general and reading and spelling at 2 years. Maternal age (older) associated with higher scores on some subtests; arithmetic scores and perceptual motor scores well below norms 2 years after HCT
Zajac Spychala [23]	14 children with ALL; HCT from 2002–2012; compared to 15 children given prophylactic CNS irradiation; 16 patients newly diagnosed with ALL (control)	Single-center, mixed methods	MRI; WISC, RAVLT, others	Median time from therapy completion (HCT or CNS irradiation): 62 months (range, 37–86)	HCT patients had more pronounced MRI findings, lower cognitive performance as compared to nonHCT patients and controls
Phipps [85]	268 children with malignant or nonmalignant diseases; HCT from 1991–1999	Single-center, prospective	Bayley, WPPSI-R, WISC-R, WISC-III, WAIS-R, WRAT-III	Pre-HCT; post-HCT at 1, 3, and 5 years	Third report of this cohort; IQ scores low at baseline but generally stable over 5 years. Age not significant factor, contradicting prior report. TBI, unrelated donor HCT, prior CNS therapy and acute GVHD significant but likely not very relevant. SES is the strongest predictor of outcomes.

MRI indicates magnetic resonance imaging.

* Measures referred to in table are listed here: Bayleys Scale of Infant Development, Stanford-Binet intelligence scales, Wechsler Intelligence Scale for Children (WISC-R, WISC-III, WISC-IV), Vineland Adaptive Behavior Scales, Wide Range Achievement Test (WRAT-R, WRAT-III), Developmental Test of Visual-Motor Integration (VMI, VMI-4), California Verbal Learning Test (CVLT or CVLT-C), Connors' continuous performance test, Purdue Pegboard Test, Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II), Tests of Variables of Attention (TOVA), Adaptive Behavior Assessment System (ABAS), Woodcock-Johnson III Tests of Achievement (WJ III ACH), Wechsler Adult Intelligence Scale (WAIS-R or WAIS-IV); Wide-range Assessment of Memory and Learning (WRALM2), Rey Auditory Verbal Learning Test (RAVLT).

Table 3**Areas for Possible Future Studies To Address**

Methods of neurocognitive assessment
Appropriate measures for test/retest and domains to be covered
Clinically relevant biomarkers (as appropriate)
Adjusting for differences in treatment exposures
Appropriate assessments for patients experiencing
Prior chemotherapy (or radiation)
Prior HCT
Prior CAR-T
CRS
ICANS
GVHD
Neurological complications (e.g., stroke)
Development of consensus measures to capture specific domains at baseline and at established timepoints. Baseline testing should include core cognitive domains
Timing of neurocognitive assessments
The need for longitudinal evaluations (development/use of consensus measures to capture specific domains at baseline and at established timepoints)
Mapping interpretation of cognitive change
Extending commonly used timepoints to the CAR-T indication, and to a lesser degree, HCT
Therapy-related
Characterization or comparison of neurocognitive late effects after CD19+ directed therapies including CAR-T and Blinatumomab
Comparison of late effects profiles of targeted therapies based on cellular vehicle and construct
Understanding the role of autoimmunity in neurocognitive late effects after HCT, checkpoint inhibitors, or cellular therapies
Challenges
The interpretation and prognostic role of neuroimaging in this population
Standardization of neurological injury grading across CAR-T trials sequelae should be brief, easy to administer, and conducted at the beginning of treatment
Comparing outcomes in populations with ages extending from early childhood to young adulthood.
Addressing test/retest and practice effects
Barriers to assessment, including distance from treatment centers to home, health professionals capable and available to complete assessments

Proposed Cognitive Domains and Potential Subtests for HSCT and CAR T-Cell Therapy Research Studies

Table 4

Domains to be Assessed	COG Trials*	Non-COG Studies
Intellectual Functioning	WPPSI-IV/WISC-V/WAIS-IV Block Design, Matrix Reasoning	WASI-II Block Design, Matrix Reasoning, Similarities
Attention/Working Memory	WPPSI-IV Picture Memory, Zoo Locations or WISC-V/WAIS-IV Digit Span; Cogstate Attention Task; Cogstate Working Memory Task	WISC-V/WAIS-IV Digit Span; NIH Toolbox Flanker
Processing Speed	WPPSI-IV Animal Coding, Bug Search or WISC-V/WAIS-IV Coding, Symbol Search; Cogstate Processing Speed Task	WPPSI-IV Animal Coding, Bug Search or WISC-V/WAIS-IV Coding, Symbol Search; Trail Making Test A
Language	WPPSI-IV/WISC-V/WAIS-IV Vocabulary	WASI-II Vocabulary; EVT-2 or EOWPVT; NIH Toolbox Picture Vocabulary Test; DKEFS Verbal Fluency Test
Memory	CMS Stories or WMS-IV Logical Memory; CVLT-C/CVLT-3; Cogstate Learning Task	CMS Stories/WMS-IV Logical Memory; CVLT-C/CVLT-3; NIH Toolbox Picture Sequence Memory Test; MEMRY
Executive Functioning	Cogstate Groton Maze Learning Task; BRIEF-P/BRIEF-2/BRIEF-A	Trail Making Test B; NIH Toolbox DCCS; BRIEF-P/BRIEF-2/BRIEF-A
Academic Achievement	Not applicable	WRAT-5

* All subtests identified are included within the ALTE07C1 battery or Cogstate Master Build; Wechsler Preschool and Primary Scales of Intelligence, Fourth Edition (WPPSI-IV); NIH Toolbox; Cogstate; Wechsler Intelligence Scale for Children (WISC-V); Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II); Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV); Behavior Rating Inventory of Executive Function, Preschool Version (BRIEF-P); Behavior Rating Inventory of Executive Function, Second Edition (BRIEF-2); Behavior Rating Inventory of Executive Function, Adult Version (BRIEF-A); Expressive Vocabulary Test, Second Edition (EVT-2); California Verbal Learning Test, Children's Version (CVLT-C); California Verbal Learning Test, Third Edition (CVLT-3); Multidimensional Everyday Memory Ratings for Youth (MEMRY); Delis-Kaplan Executive Function System (DKEFS); Expressive One Word Picture Vocabulary Test (EOWPVT); Children's Memory Scales (CMS); Wechsler Memory Scales, Fourth Edition (WMS-IV); Wide Range Achievement Test, Fifth Edition (WRAT-5).