SPECIAL SERIES: NEUROCOGNITIVE OUTCOMES IN SURVIVORS OF PEDIATRIC CANCER

Assessment and Monitoring of Neurocognitive Function in Pediatric Cancer

Lisa M. Jacola, PhD[1]; Marita Partanen, PhD[2]; Jurgen Lemiere, PhD[3]; Melissa M. Hudson, MD[1]; and Sophie Thomas, PhD[4]

Cognitive late effects are among the most common life-altering sequelae of childhood cancer, with reported prevalence ranging from 35% to 60% depending on specific diagnostic and treatment groups.[1,2] For the proportion of survivors that experience cognitive late effects, the functional impact of these difficulties increases over time and predisposes survivors to difficulties with educational achievement, vocational status, and independent living.[3,4] Prospective, longitudinal research studies evaluating neurocognitive outcomes in survivors of childhood acute lymphoblastic leukemia (ALL) and childhood medulloblastoma show that treatment-related neurocognitive deficits present during treatment and negatively affect outcomes such as academic achievement, educational attainment, and quality of life throughout survivorship.[5-10]

The Psychosocial Standards of Care Project for Childhood Cancer guidelines emphasize the importance of systematic and interdisciplinary assessment of neurocognitive and psychosocial healthcare needs that begins during treatment.[11,12] Specific to neurocognitive monitoring, the Psychosocial Standards of Care Project for Childhood Cancer guidelines describe a risk-stratified approach beginning during treatment.[13] Neurocognitive assessment is also recommended by long-term follow-up (ie, at least 2 years after completion of therapy) guidelines for survivors treated with CNS-directed therapies (eg, cranial irradiation and intrathecal chemotherapy).[14-16]

Despite the clinical relevance of longitudinal follow-up, establishing such a program can be challenging. Traditional neuropsychology services are most appropriate for referral questions that involve diagnostic conceptualization and individualized recommendations to remediate existing deficits. These time- and resource-intensive models are impractical to implement at the population level, and not all survivors need this level of care. Strategies for screening in pediatric oncology should be feasible to implement across settings and carefully designed to ensure that service quality is maintained. We provide a pragmatic, evidence-based framework for neurocognitive monitoring that begins during therapy and continues into survivorship. We present a systematic approach with the potential for application across diverse clinical settings that considers varying availability of resources as well as cultural differences. This approach incorporates elements of preventative screening models from the broader pediatric population placed in the context of findings from pediatric oncology populations.

PREVENTION-BASED MODELS FROM PEDIATRIC POPULATIONS

Prevention-based models from general pediatric or educational settings typically include multiple levels of support, which increase in intensity based on the needs of the individual child.[17,18]

Hardy et al[19] proposed a prevention-based, tiered, three-level approach to neuropsychological assessment. The prevention-based model proposed by Hardy et al[19] is a notable advancement in the field and provides a basis for a tiered neuropsychological assessment. We build on this model by (1) specifying direction for implementation in pediatric oncology, (2) addressing application of monitoring across contexts (eg, countries that do not have access to computerized measures), and (3) offering a common language to improve intradisciplinary and interdisciplinary communication.

NEUROCOGNITIVE MONITORING FOR PEDIATRIC ONCOLOGY: PROPOSED MODEL

Our proposed three-level model for neurocognitive monitoring that starts during cancer-directed therapy is depicted in Figure 1. The primary level is intended for all pediatric oncology patients within a clinical service, irrespective of cognitive complaints or risk factors. The secondary level is for patients with subjective cognitive complaints, those who present with risk factors for neurocognitive difficulty, and/or those who performed poorly at the first level. The tertiary level is for patients with preexisting neurocognitive deficits or vulnerabilities and those for whom a comprehensive assessment is warranted based on the referral question (ie, differential diagnosis, individualized treatment, or educational planning), and/or those who performed poorly on earlier levels.

Figure 2 illustrates the decision-making process using the model. Starting during treatment, a provider asks

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on December 23, 2020 and published at ascopubs.org/journal/jco on April 22, 2021: DOI https://doi.org/10.1200/JCO.20.02444

© 2021 by American Society of Clinical Oncology

CONTEXT

Key Objective

We present a tiered model of neuropsychological care for childhood cancer survivors.

Knowledge Generated

The Psychosocial Standards of Care Project for Childhood Cancer guidelines highlight the need for systematic and interdisciplinary neurocognitive assessment that begins during treatment. This approach emphasizes feasibility in settings with varying resources and among culturally diverse patients and families, while maintaining a high level of service quality.

Relevance

Neurocognitive late effects are common and life-altering sequelae of childhood cancer, which have potential adverse effects on educational and vocational attainment, and social integration. Regular monitoring of neurocognitive functioning can facilitate early detection of problems and early intervention to improve quality of life. The developmental perspective of this model is crucial because neurotoxic agents and/or treatment complications can have an adverse and longstanding impact on developing neural systems.

the first question of “does the patient have known risk factors or cognitive complaints?” and moves to the next part based on their answer. For example, if a patient has no known risk factors or cognitive complaints, they complete a primary level assessment. If impairments are identified from the primary-level assessment, a higher-level assessment can be performed to obtain more detailed information. The patient can be reassessed at the secondary level at a predefined period (eg, 1 or 2 years or transition), and if they do not have further impairments, their next assessment can remain at the primary level. The dashed arrows indicate reassessments that occur over time. Decision making is informed by the presence or severity of risk factors and clinical judgment. For example, patients with significant preexisting attention, cognitive, or learning vulnerabilities may require a more comprehensive

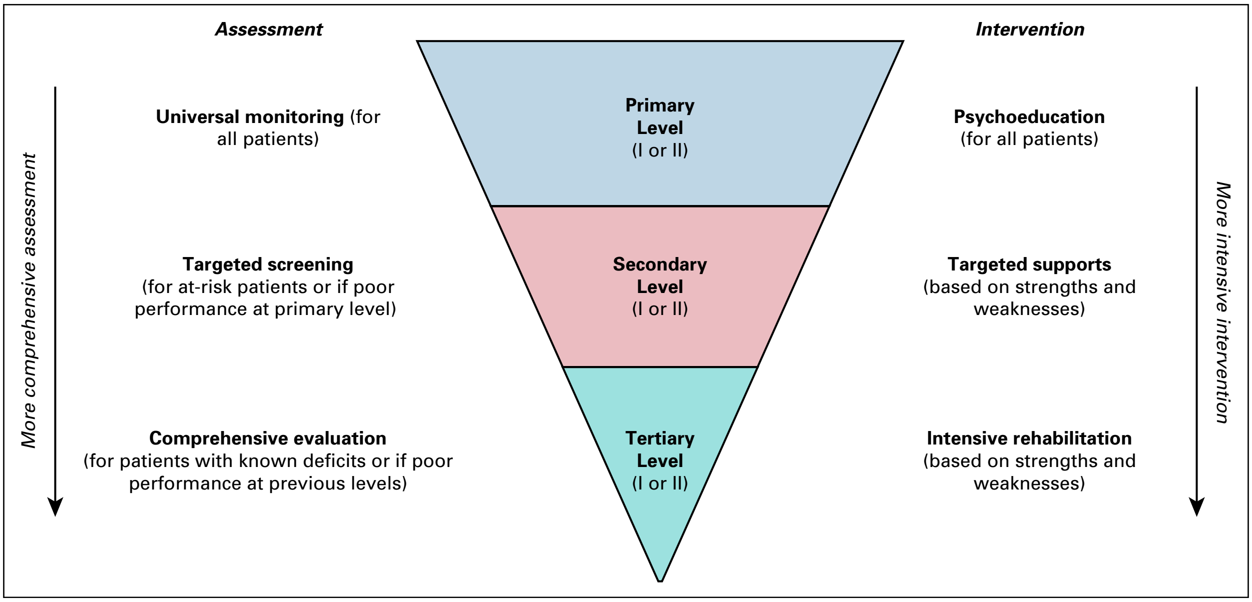

FIG 1. A model for neurocognitive monitoring in pediatric oncology. The primary level is intended for all pediatric oncology patients within a clinical service. The secondary level is for patients with subjective cognitive complaints, those who performed poorly at the first level, and those with significant disease- or treatment-related risk factors. The tertiary level is for patients with preexisting neurocognitive deficits or vulnerabilities, and those for whom a more comprehensive assessment is warranted based on the referral question (ie, differential diagnosis, individualized treatment or educational planning), or those who performed poorly on initial screening. Decision making is additionally informed by the presence or severity of risk factors, available resources, and clinical judgment, and may change over time according to patient need. The desired intervention may also inform level assignment; for example, all patients will likely benefit from psychoeducation, but only those with clear functional impairment may need individualized services, such as rehabilitation or educational planning.

approach to assessment at each time point, to adequately inform plans for education and rehabilitation services. The appropriate level of service for an individual patient may also change over time, as problems resolve or new issues emerge. For example, a patient who experiences a significant neurologic event during treatment may be assessed more frequently during recovery. The desired intervention may also inform level assignment; for example, all patients will likely benefit from psychoeducational services, but only those with clear functional impairment may need individualized services, such as rehabilitation or educational planning.

Each individual institution's approach to triage or escalation may vary according to resource availability, while ensuring that patient needs are appropriately met. For example, well-resourced centers may assess all patients known to be at high risk of impairment at secondary level, whereas less well-resourced centers may need to be reliant on screening to identify those with the greatest need. In some cases, referral outside of the hospital service may be required. Alternatively, this model and the associated evidence for a risk-stratified approach to monitoring may be used to justify additional resource requirements.

RISK ASSESSMENT

A full review of all contributing factors is outside of the scope of this article and will be covered in other manuscripts within this issue; however, it is important to note that variability in neurocognitive outcomes is not solely explained by clinical or treatment factors. Consideration of risk factors for neurocognitive difficulties may be particularly useful for triage and allocation of services in centers with limited resources. Examples are discussed below and depicted in Figure 3.

Individual Risk Factors

Longitudinal studies in survivors of childhood brain tumors show that younger age at diagnosis predicts decline in neurocognitive performance over time after accounting for CNS treatment intensity.[8] Younger age at diagnosis has been identified as a risk factor for in a large, prospective, longitudinal study of children treated for low-, standard-, and high-risk ALL[6] and in a large, prospective, cross-sectional study of children treated for high-risk ALL.[20] Other cross-sectional studies have not found this relationship, likely because of limitations such as small sample size and limited sample representativeness.[21-23] Early childhood is a critical period for neurodevelopment. Neurodevelopmental changes during early childhood include changes in the efficiency and directionality of white matter connections throughout the brain.[24] Results from neuroimaging studies in survivors of childhood ALL document brain changes, including decreased white matter integrity, that are associated with treatment intensity.[25] Younger age at diagnosis may also increase risk because of missed opportunities for social interaction during critical periods for neurodevelopment.

Survivors with preexisting neurodevelopmental conditions or cognitive impairment may also be particularly vulnerable to cancer-related cognitive dysfunction. For example, survivors of low-grade glioma with neurofibromatosis type 1[26] and survivors of ALL with Down syndrome[27] have worse neurocognitive outcomes compared to peers without a cancer history.

Clinical Risk Factors

Individuals with primary or metastatic CNS neoplasms as well as those whose treatment requires CNS-directed therapy are at greatest risk for late effects.[28-30] Studies in survivors of childhood ALL have identified bacteremia or sepsis[31] and acute methotrexate neurotoxicity[32] as factors that add to treatment-related risk for neurocognitive deficits. In childhood brain tumor, posterior fossa syndrome[10] and treatment-induced ototoxicity[33] increase risk for deficits in global intellectual functioning and academic achievement. Elements of supportive care, such as repeated exposure to general anesthesia for diagnostic or therapeutic procedures, have also been linked to neurocognitive late effects.[34,35]

Environmental Risk Factors

The impact of environmental factors is illustrated by studies of noncancer and childhood cancer populations that document the adverse impact of low socioeconomic status on brain development and cognitive outcomes.[20,36] Modifiable lifestyle factors that contribute to neurocognitive difficulties should also be included in risk assessment, as these represent opportunities for intervention. For example, long-term survivors of childhood ALL report significant fatigue and sleep disturbance that is predictive of poorer neurocognitive outcomes.[37]

As risk factors may change over time, systematic reassessment based on review of the medical record and patient or family report is important. The Children's Oncology Group Long-Term Follow-Up Resource Guide includes examples of treatment summaries and psychosocial assessment tools that can be used as starting points for the development of an institution-specific risk screening form for on-therapy patients.[38] The Psychosocial Assessment Tool 2.0 is an example of a practical tool for screening psychosocial risk and resiliency factors that has been validated in families of children with cancer.[39] The Psychosocial Assessment Tool 2.0 can be used to screen for factors that increase risk for poorer psychosocial and neurocognitive outcomes, and might otherwise be overlooked in an oncology-focused assessment (eg, preexisting neurodevelopmental conditions, family history, and socioeconomic factors).

MEASUREMENT

At the institutional level, implementation of models for cognitive surveillance requires pragmatic consideration of discrepancies in local service provision. This in turn necessitates acknowledgment of wide variation in resource

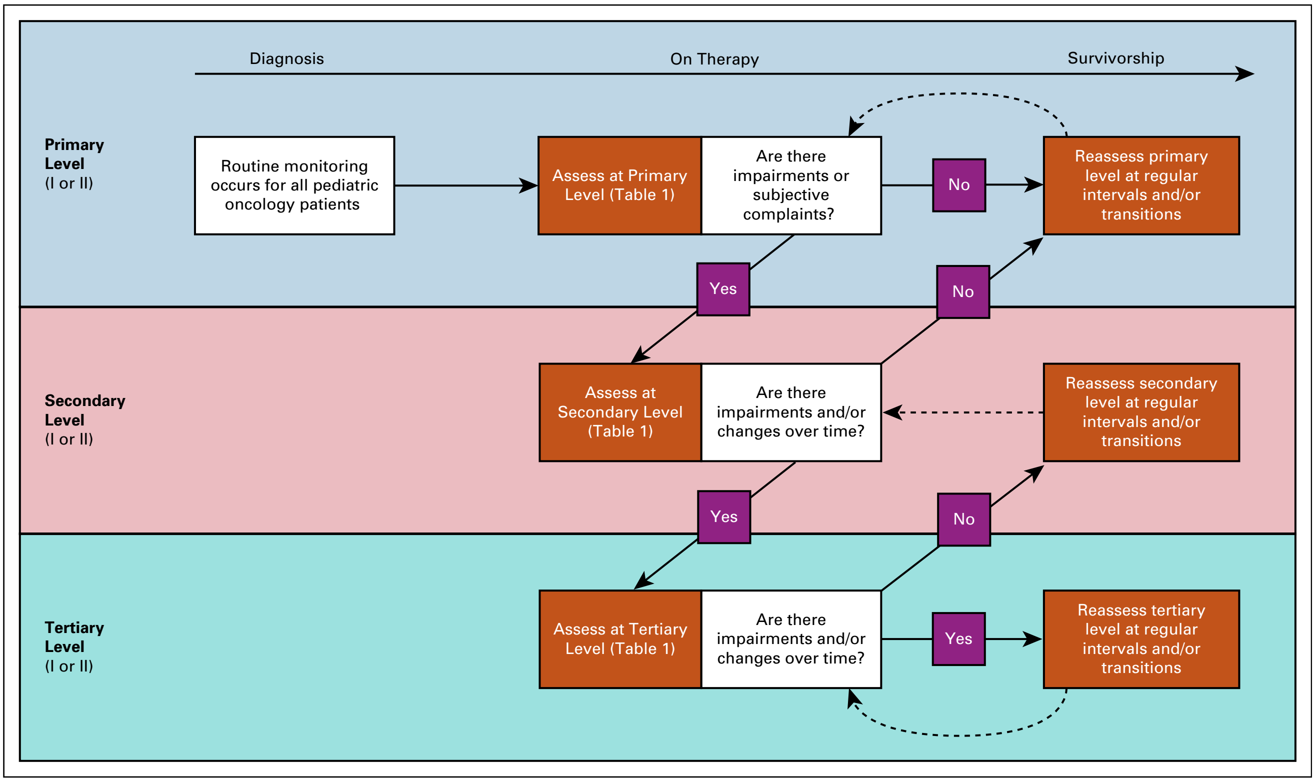

FIG 2. Implementing the model with risk-stratified decision making. Decision making is risk stratified and iterative, and strategies for model implementation are meant to be flexible in consideration of changing patient needs and available resources (ie, personnel, time, and materials). There is flexibility to increase or decrease levels of support based on data and clinical judgment, or to skip levels based on severity of need. Starting during treatment, a provider asks the first question of "does the patient have known risk factors or cognitive complaints?" and moves to the next part based on their answer. For example, if a patient has no known risk factors or cognitive complaints, they complete a primary-level assessment. If impairments are identified from the primary-level assessment, a higher-level assessment can be completed to obtain more detailed information. The patient can be reassessed at the secondary level at a predefined period (eg, 1 or 2 years or transition), and if they do not have further impairments, their next assessment can remain at the primary level. The dashed arrows indicate reassessments that occur over time.

availability. Not all centers have access to a qualified psychologist or a full range of cognitive tests, and psychologists may also have time constraints associated with a large service volume. Furthermore, centers in the United States will have at their disposal the Cogstate battery for screening but this is not yet widely used elsewhere, and thus we have recommended a no-cost alternative question-based screening. This also provides a cost-free alternative for screening all pediatric oncology patients as it is acknowledged that not all centers will be in a position to undertake formal assessment with all patients.

It is important to recognize the clinical and research utility of neurocognitive assessment in the proposed model. Results inform care of an individual patient and advances knowledge to guide development of preventative and remedial interventions. Collaboration from multidisciplinary teams should be emphasized in development and implementation of a screening model. Measures must have documented psychometric characteristics, and constraints related to longitudinal testing (eg, practice effects)[40] and monitoring children across age categories (eg, limited test options) need to be recognized. Vulnerable neurocognitive domains, such as sustained attention, processing speed, and executive function, cannot be assessed in very young children (eg, the majority of patients with ALL). Variability in scores on repeat testing can be because of a combination of true score change and practice effects (ie, increased efficiency because of familiarity with the test, and remembering actual items on the test).[40,41] Careful consideration of the test-retest interval is necessary, and this differs widely based on the specific test. Batteries such as Cogstate are designed to be repeated at short intervals and can be more suitable for regular monitoring programs, but more traditional gold-standard tests are not, although the latter are often more available and accepted in clinical settings. We have acknowledged the importance of being pragmatic in recognizing those tests that are widely and cross culturally accepted, such as Wechsler tests, in contrast to those that may have demonstrated sensitivity in a research setting but do not have wide availability, familiarity, or acceptability. Input from a multidisciplinary team that includes psychologists and/or neuropsychologists is important when determining both tests to implement locally at each level and time point for repeat testing.

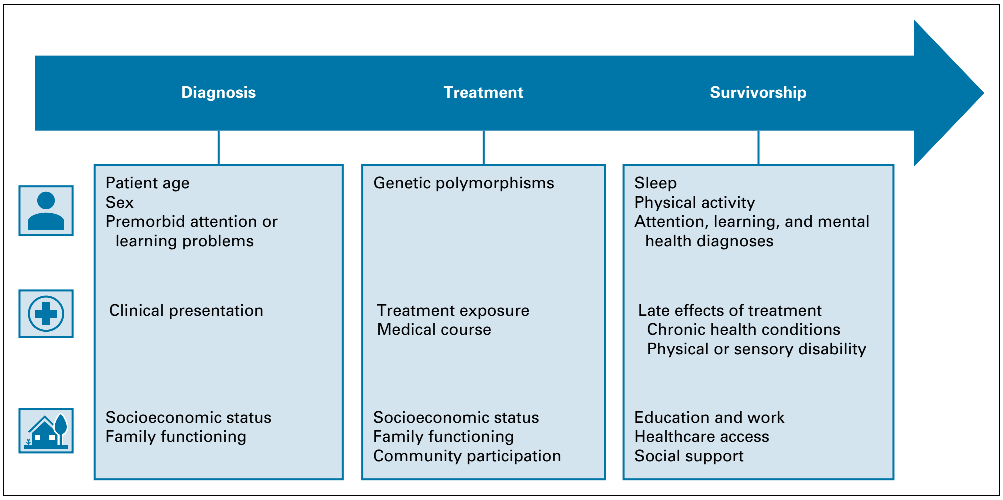

FIG 3. Factors contributing to neurocognitive outcomes. Individual, clinical, and environmental factors should be considered in decision making with the proposed model. Factors are presented according to the time that is most relevant. Risk assessment is an iterative process.

Additionally, there can be limitations in test availability for a patient's native language or for assessment measures that are appropriate for a patient's race, ethnic, cultural, or immigration background; the development of such measures is a priority for research. Considerable efforts to identify measures suitable for administration across a wide variety of languages and cultures have been undertaken by the European Society of Paediatric Oncology Brain Tumour Quality of Survival group.[42] This process identified a set of cognitive tests and quality of survival patient-reported outcome measures to address the domains considered most crucial for long-term follow-up in childhood brain tumor trials.[43] This flexible approach balances the importance of a minimum core data set while offering the flexibility to augment this battery with a more comprehensive plus range of tests as permitted by local resources. Again, this is based on pragmatic acceptance of tests that are available and acceptable in a wide range of countries. More recently, a hierarchical approach to the battery has been recommended, where those tests considered most crucial are requested to be administered first to encourage a consistent minimum data set.[43]

This core plus model with a specified test hierarchy is conceptually similar to the tiered model of Hardy et al[21] and shares the feature of progressing through levels of more detailed assessment according to time and resources. However, the Hardy et al[19] model, which is designed with an explicit clinical focus, demonstrates greater definition between the levels, which can include a different medium of testing and user qualification. The model also focuses on progression through levels based on patient need and results obtained at each level. We incorporated aspects of the core and core plus approaches in the implementation of our model, as detailed in Table 1. For example, the core measures provide a targeted assessment and can be included as a secondary- or tertiary-level assessment, depending upon resource availability and culturally accepted practices.

Even with the identification of a common set of internationally used measures, cognitive assessment in an acute hospital context can be challenging. Fluctuations in patient health status and symptom burden must be considered in the timing of and approach to assessment, as well as interpretation of findings. Patients and families may experience psychosocial distress during treatment, which could limit the clinical utility of results. Flexibility is essential, and a single detailed test battery is unlikely to be applicable in all contexts.

The measures detailed in Table 1 are recommended with consideration of the above-described challenges. We include caregiver ratings and, when feasible, direct performance measures that are appropriate for young children. There is a balance between measures that are sensitive to early changes and those that are familiar and thus locally acceptable and also those that are clinically useful for providing guidance to clinicians, families, and educational systems. Any of the more global measures contain subtests that measure discrete neurocognitive skills previously identified as vulnerable in the literature (eg, working memory and processing speed). Similar to guidelines from the core plus model, measures should be chosen according to resource availability, feasibility, and acceptability specific to that country or center.

DISCUSSION

In this paper, we present a preventative, tiered model of neuropsychological care to identify and support children who are at risk for neurocognitive deficits related to pediatric cancer or its treatment. Regular monitoring facilitates detection of patterns of change in cognitive domains. Additionally, identification of cognitive problems before

TABLE 1. Assessment and Intervention Within the Tiered Model

Level	Assessment	Suggested Measures	Intervention
Risk factors		Medical record review, treatment summaries, and PAT 2.0[39]	
Primary	**Open-ended questions**		**Psychoeducation**
	School or work	How is school or work going (grades, attendance, and needing support)? Changes?	Developmental milestones
	Social	How are they getting along with others? Changes?	Neurocognitive late effects
	Mood and behavior	What is their mood or behavior like? Changes?	Strategies for adaptive skills
	Adaptive skills	Independence with dressing, chores, transportation, and adherence? Changes?	Center-specific resources
	Standardized questionnaires		
	Adaptive skills	ABAS-3[45]	
	Attention and executive function	Conners-3 Short Form[46]; BRIEF-2 Screening Form[47]	
	Mood and behavior	SDQ[48,49]; CBCL[50]; PROMIS Short Form[51,52]	
	Performance measures		
	Attention, processing speed, and executive function	NIH Toolbox[52,53]; ImPACT[54,55]; Cogstate[56,57]; Attention Network Test[58]	
Secondary	**Standardized questionnaires**[a]		**Targeted supports**
	Early development	DAYC-2[59]; Mullen Scales of Early Learning[60]	Eligibility for early intervention (eg, early intervention program)
	Adaptive skills	Vineland-3 Rating or Interview Forms[61]; SIB-R Rating or Interview Forms[62]	Monitor developmental progress
	Attention and executive function	Conners-3 Long Form; BRIEF[47,63,64]	School reentry
	Mood and behavior	BASC-3[65]; PROMIS Full Form[51,52]	Academic supports (eg, Section 504 plan and individualized education program)
	Performance measures—core cognitive[a]		Round-table or academic meetings
	Estimated IQ	Wechsler Scales—Abbreviated IQ (WASI-II, WISC-V, WAIS-IV)[66,67,69]	Transition planning
	Verbal intelligence	Wechsler Scales—Vocabulary (WASI-II, WISC-V, WAIS-IV); Receptive Vocabulary (WPPSI-IV)[68]	
	Fluid intelligence	Wechsler Scales—Matrix Reasoning (WASI-II, WISC-V, WAIS-IV, WPPSI-IV)	
	Working memory	Wechsler Scales—Digit Span (WISC-V, WAIS-IV); Picture Memory (WPPSI-IV)	
	Processing speed	Wechsler Scales—Coding, Symbol Search (WISC-V, WAIS-IV); Bug Search, Animal Coding (WPPSI-IV)	
	Visual spatial	WRAVMA[70]; Beery VMI-6[71]	
	Preacademic or academic	BBCS-3:R—School Readiness Composite[72]; WIAT-3 Word Reading[73]	
Tertiary	**Standardized questionnaires**[a]		**Rehabilitation services**
	Adaptive skills	Multiple rater forms	School reentry
	Attention and executive function		Formalized academic supports
	Mood and behavior		Behavior intervention plans
	Performance measures—core plus[a,b]		Transition planning
	Global cognitive functioning	Wechsler Scales–Full Scale IQ (WASI-2, WPPSI-IV, WISC-V, WAIS-4)	
	Sustained attention	KCPT-2[74]; CPT-3[75]; TEA-Ch 2[76]	**Differential diagnosis**
	Executive Function	DKEFS Verbal Fluency, Color-Word Interference, and Trail Making Test, 20 Questions[77]	
		NEPSY-II Verbal Fluency, Rapid Naming, Auditory Attention and Response Set[78]	**Treatment planning**
	Learning and memory	CMS[79]; WMS-IV[80]; CVLT-C/3[81,82]; RAVLT[83]; RCFT[84]; ChAMP[85]	
	Academics	WIAT-3 Spelling, Numerical Operations, Reading Fluency, Math Fluency, Writing Fluency	

NOTE. Bold indicates broad category of assessment measure or intervention.

Abbreviations: ABAS-3, Adaptive Behavior Assessment System, 3rd Edition; BASC-3, Behavior Assessment System for Children; BBCS-3:R, Bracken Basic Concepts Scale, 3rd Edition:Receptive; Beery VMI-6, Beery-Buktenica Developmental Test of Visual Motor Integration; BRIEF, Behavior Rating Inventory of Executive Function; BRIEF-2, Behavior Rating Inventory of Executive Function, 2nd Edition; CBCL, Child Behavior Checklist; ChAMP, Children and Adolescent Memory Profile; CMS, Children's Memory Scales; Conners-3, Conners 3rd Edition; CPT-3, Conners' Continuous Performance Test, 3rd Edition; CVLT-3, California Verbal Learning Test, 3rd Edition; Conners Kiddie Continuous Performance Test, 2nd Edition; CVLT-C, California Verbal Learning Test for Children; DAYC-2, Developmental Assessment of Young Children, 2nd Edition; DKEFS, Delis Kaplan Executive Function System; ImPACT, Immediate Post-Concussion Assessment and Cognitive Testing; NEPSY-II, A Developmental Neuropsychological Assessment, 2nd Edition; NIH-toolbox, National Institutes of Health Toolbox; PAT 2.0, Psychosocial Assessment Tool, Version 2.0; PROMIS, Patient Reported Outcomes Measurement System; RAVLT, Rey Auditory Verbal Learning Test; RCFT, Rey Complex Figure Test; SDQ, Strengths and Difficulties Questionnaire; SIB-R, Scales of Independent Behavior—Revised; TEA-Ch2, Test of Everyday Attention for Children, 2nd Edition; Vineland-3, Vineland Adaptive Behavior Scales, 3rd Edition; WAIS-IV, Wechsler Adult Intelligence Scales, 4th Edition; WASI-II, Wechsler Abbreviated Scales of Intelligence, 2nd Edition. WIAT-3, Wechsler Individual Achievement Test, 3rd Edition; WISC-V, Wechsler Intelligence Scales for Children, 5th Edition; WMS-IV, Wechsler Memory Scales, 4th Edition; WPPSI-IV, Wechsler Preschool and Primary Scales of Intelligence, 4th Edition; WRAVMA, Wide Range Assessment of Visual Motor Abilities.

[a] In addition to previous level(s).

[b] Most likely to be augmented based on clinical referral question. Assessment approaches may be modified in consideration of resources; we offer multiple modalities at each level for this reason. Not all measures have language or cultural translations; in these cases, local tests that measure the same domain can be substituted. Many standardized questionnaires have versions for multiple raters (parent or caregiver, self, and teacher). Rater selection for questionnaire measures may differ in consideration of patient age and level of assessment. It is common to include information from external raters at the tertiary level.

their impact on daily functioning facilitates remedial opportunities that can translate into improved outcomes and quality of life. The developmental perspective of this model is crucial because potentially neurotoxic agents and/or treatment complications can have an adverse and longstanding impact on developing neural systems and everyday functioning.

Our model is built on the growing evidence that multiple risks factors can affect cognitive development. Insight into these risk factors is crucial to determining when neuropsychological monitoring should be initiated. Defining the level of assessment based on the risk algorithm is beneficial but challenging as large individual variation exists. To deal with these variations, our model emphasizes the need to be flexible based on existing risk factors, but also on clinical need. For example, some risk factors can be considered as a red flag to commence follow-up on the secondary level (eg, brain tumor, cranial irradiation, or young age at treatment) where resources allow.

The interval between assessments should be flexible depending on risk factors, clinical needs, and test properties for repeat testing. Assessment should be prioritized in patients with significant reported or observed changes in behavior, cognition, or academic performance. Good clinical practice dictates screening by pediatric oncologists for cognitive problems on a regular basis during treatment and following completion of therapy. The rationale to undertake an early assessment before or during treatment is also driven by evidence that early interventions during the cancer treatment could be beneficial and durable.[44] The last article of this Special Issue outlines the evidence base for interventions to remediate or improve functioning.

Neurocognitive problems contribute to a core component of quality of life for a significant proportion of pediatric cancer survivors. Good clinical care requires neuropsychological follow-up and interventions. By providing this preventative tiered model, we hope to inspire pediatric oncologic centers to allocate time and resources to incorporate or expand neuropsychology services in their local program. Recognizing the reality that neuropsychological resources in pediatric oncology centers are often limited, we outline minimum requirements on each level. Ideally, a neuropsychologist is available at each pediatric oncology center to advice about the frequency of monitoring for each child. In centers lacking neuropsychological resources, a brief cognitive screening can be administered during routine follow-up by the pediatric oncologist. In this case, collaborations with specialized neuropsychological units for children that require follow-up on secondary or tertiary levels are advisable.

Our model proposes a systematic approach for monitoring neuropsychological functioning within a broader framework of psychosocial care. Monitoring of neurocognition should not occur independent of a broader psychosocial evaluation.

Our model is based on a synthesis of current evidence-based knowledge but will need refinement as new research provides insight into the complex interactions between pediatric cancer, its treatment, the developing brain of the treated child, and the role of the environment. Systematic evaluation of the proposed model across pediatric oncology settings is needed to inform generalizability. Further work investigating neurocognitive outcomes and risk factors in the broader pediatric oncology population can be used to inform risk-stratified decision making. Additional work is needed to establish the clinical utility of computerized assessment measures for identifying neurocognitive vulnerabilities and changes over time, as well as the validity of assessment measures across culturally diverse groups.

AFFILIATIONS

[1]St Jude Children's Research Hospital, Memphis, TN
[2]Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands
[3]University Hospital Leuven, Leuven, Belgium
[4]Nottingham Children's Hospital, Nottingham, United Kingdom

CORRESPONDING AUTHOR

Lisa M. Jacola, PhD, ABPP-CN, Department of Psychology, St Jude Children's Research Hospital, 262 Danny Thomas Place, MS 740, Memphis, TN 38105; e-mail: lisa.jacola@stjude.org.

DISCLAIMER

The content is solely the responsibility of the authors and does not necessarily represent the official views of NIH.

SUPPORT

Support was provided by the NIH National Cancer Institute grants(s) (P30-CA21765 and GM92666 to St Jude Children's Research Hospital) and the American Lebanese Syrian Associated Charities (ALSAC).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.20.02444.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

REFERENCES

1. Alvarez JA, Scully RE, Miller TL, et al: Long-term effects of treatments for childhood cancers. Curr Opin Pediatr 19:23-31, 2007
2. 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 24:653-663, 2015
3. Crom DB, Lensing SY, Rai SN, et al: Marriage, employment, and health insurance in adult survivors of childhood cancer. J Cancer Surviv 1:237-245, 2007
4. Gurney JG, Krull KR, Kadan-Lottick N, et al: Social outcomes in the childhood cancer survivor study cohort. J Clin Oncol 27:2390-2395, 2009
5. Jacola LM, Edelstein K, Liu W, et al: Cognitive, behaviour, and academic functioning in adolescent and young adult survivors of childhood acute lymphoblastic leukaemia: A report from the childhood cancer survivor study. Lancet Psychiatry 3:965-972, 2016
6. Jacola LM, Krull KR, Pui CH, et al: Longitudinal assessment of neurocognitive outcomes in survivors of childhood acute lymphoblastic leukemia treated on a contemporary chemotherapy protocol. J Clin Oncol 34:1239-1247, 2016
7. Kunin-Batson A, Kadan-Lottick N, Neglia JP: The contribution of neurocognitive functioning to quality of life after childhood acute lymphoblastic leukemia. Psychooncology 23:692-699, 2014
8. 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 27:3691-3697, 2009
9. Schreiber JE, Gurney JG, Palmer SL, et al: Examination of risk factors for intellectual and academic outcomes following treatment for pediatric medulloblastoma. Neuro Oncol 16:1129-1136, 2014
10. Schreiber JE, Palmer SL, Conklin HM, et al: Posterior fossa syndrome and long-term neuropsychological outcomes among children treated for medulloblastoma on a multi-institutional, prospective study. Neuro Oncol 19:1673-1682, 2017
11. Wiener L, Kazak AE, Noll RB, et al: Standards for the psychosocial care of children with cancer and their families: An introduction to the special issue. Pediatr Blood Cancer 62:S419-S424, 2015 (suppl 5)
12. Wiener L, Kazak AE, Noll RB, et al: Interdisciplinary collaboration in standards of psychosocial care. Pediatr Blood Cancer 62:S425, 2015 (suppl 5)
13. Annett RD, Patel SK, Phipps S: Monitoring and assessment of neuropsychological outcomes as a standard of care in pediatric oncology. Pediatr Blood Cancer 62:S460-S513, 2015 (suppl 5)
14. Children's Oncology Group: Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. Version 5.0, October, 2018. http://www.survivorshipguidelines.org/pdf/2018/COG_LTFU_Guidelines_v5.pdf
15. Scottish Intercollegiate Guidelines Network (SIGN): Long term follow up of survivors of childhood cancer, March, 2013. https://www.sign.ac.uk/media/1070/sign132.pdf
16. Dutch Childhood Oncology Group: Guidelines for follow-up in survivors of childhood cancer 5 years after diagnosis, 2010. https://www.skion.nl/workspace/uploads/vertaling-richtlijn-LATER-versie-final-okt-2014_2.pdf
17. Gilleland J, Reed-Knight B, Brand S, et al: Assessment of family psychosocial functioning in survivors of pediatric cancer using the PAT2.0. Psychooncology 22:2133-2139, 2013
18. Preston AI, Wood CL, Stecker PM: Response to intervention: Where it came from and where it's going. Preventing Sch Fail 60:173-182, 2015
19. Hardy KK, Olson K, Cox SM, et al: Systematic review: A prevention-based model of neuropsychological assessment for children with medical illness. J Pediatr Psychol 42:815-822, 2017
20. Hardy KK, Embry L, Kairalla JA, et al: Neurocognitive functioning of children treated for high-risk B-acute lymphoblastic leukemia randomly assigned to different methotrexate and corticosteroid treatment strategies: A report from the children's oncology group. J Clin Oncol 35:2700-2707, 2017
21. Espy KA, Moore IM, Kaufmann PM, et al: Chemotherapeutic CNS prophylaxis and neuropsychologic change in children with acute lymphoblastic leukemia: A prospective study. J Pediatr Psychol 26:1-9, 2001
22. Jansen NC, Kingma A, Schuitema A, et al: Post-treatment intellectual functioning in children treated for acute lymphoblastic leukaemia (ALL) with chemotherapy-only: A prospective, sibling-controlled study. Eur J Cancer 42:2765-2772, 2006
23. Jansen NC, Kingma A, Schuitema A, et al: Neuropsychological outcome in chemotherapy-only-treated children with acute lymphoblastic leukemia. J Clin Oncol 26:3025-3030, 2008
24. Lebel C, Walker L, Leemans A, et al: Microstructural maturation of the human brain from childhood to adulthood. Neuroimage 40:1044-1055, 2008
25. Pryweller JR, Glass JO, Sabin ND, et al: Characterization of leukoencephalopathy and association with later neurocognitive performance in pediatric acute lymphoblastic leukemia. Invest Radiol 56:117-126, 2021
26. Taddei M, Erbetta A, Esposito S, et al: Brain tumors in NF1 children: Influence on neurocognitive and behavioral outcome. Cancers (Basel) 11:1772, 2019
27. Roncadin C, Hitzler J, Downie A, et al: Neuropsychological late effects of treatment for acute leukemia in children with Down syndrome. Pediatr Blood Cancer 62:854-858, 2015
28. 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 53:108-120, 2015
29. 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 126:346-353, 2015
30. Robinson KE, Fraley CE, Pearson MM, et al: Neurocognitive late effects of pediatric brain tumors of the posterior fossa: A quantitative review. J Int Neuropsychol Soc 19:44-53, 2013
31. Cheung YT, Eskind A, Inaba H, et al: Association of bacteremic sepsis with long-term neurocognitive dysfunction in pediatric patients with acute lymphoblastic leukemia. JAMA Pediatr 172:1092-1095, 2018
32. Nassar SL, Conklin HM, Zhou Y, et al: Neurocognitive outcomes among children who experienced seizures during treatment for acute lymphoblastic leukemia. Pediatr Blood Cancer 64, 2017
33. Olivier TW, Bass JK, Ashford JM, et al: Cognitive implications of ototoxicity in pediatric patients with embryonal brain tumors. J Clin Oncol 37:1566-1575, 2019
34. Banerjee P, Rossi MG, Anghelescu DL, et al: Association between anesthesia exposure and neurocognitive and neuroimaging outcomes in long-term survivors of childhood acute lymphoblastic leukemia. JAMA Oncol doi: 10.1001/jamaoncol.2019.1094 [epub ahead of print on June 20, 2019]
35. Jacola LM, Anghelescu DL, Hall L, et al: Anesthesia exposure during therapy predicts neurocognitive outcomes in survivors of childhood medulloblastoma. J Pediatr 223:141-147.e4, 2020
36. Ronfani L, Vecchi Brumatti L, Mariuz M, et al: The complex interaction between home environment, socioeconomic status, maternal IQ and early child neurocognitive development: A multivariate analysis of data collected in a newborn cohort study. PLoS One 10:e0127052, 2015
37. Cheung YT, Brinkman TM, Mulrooney DA, et al: Impact of sleep, fatigue, and systemic inflammation on neurocognitive and behavioral outcomes in long-term survivors of childhood acute lymphoblastic leukemia. Cancer 123:3410-3419, 2017

38. Cure Search, Children's Oncology Group: Establishing and enhancing services for childhood cancer survivors: Long-term follow-up program resource guide. 2007. http://www.survivorshipguidelines.org/pdf/LTFUResourceGuide.pdf
39. Pai AL, Patino-Fernandez AM, McSherry M, et al: The psychosocial assessment tool (PAT2.0): Psychometric properties of a screener for psychosocial distress in families of children newly diagnosed with cancer. J Pediatr Psychol 33:50-62, 2008
40. Duff K, Callister C, Dennett K, et al: Practice effects: A unique cognitive variable. Clin Neuropsychol 26:1117-1127, 2012
41. Duff K, Atkinson TJ, Suhrie KR, et al: Short-term practice effects in mild cognitive impairment: Evaluating different methods of change. J Clin Exp Neuropsychol 39:396-407, 2017
42. Thomas S, Reynolds D, Morrall M, et al: The european society of paediatric oncology ependymoma-II program core-plus model: Development and initial implementation of a cognitive test protocol for an international brain tumour trial. Eur J Paediatr Neurol 23:560-570, 2019
43. Limond JA, Bull KS, Calaminus G, et al: Quality of survival assessment in European childhood brain tumour trials, for children aged 5 years and over. Eur J Paediatr Neurol 19:202-210, 2015
44. Krull KR, Hardy KK, Kahalley LS, et al: Neurocognitive outcomes and interventions in long-term survivors of childhood cancer. J Clin Oncol 36:2181-2189, 2018
45. Harrison PL, Oakland T: Adaptive Behavior Assessment System (ABAS-3) (ed 3). Torrance, CA, Western Psychological Services, 2015
46. Conners CK: Conners 3rd Edition. Toronto, ON, Multi-Health Systems, 2008
47. Gioia GA, Isquith PK, Guy SC, et al: Behavior Rating of Executive Function, Second Edition (BRIEF-2). Lutz, FL, Psychological Assessment Resource, 2016
48. Goodman R: Psychometric properties of the strengths and difficulties questionnaire. J Am Acad Child Adolesc Psychiatry 40:1337-1345, 2001
49. Strengths and Difficulties Questionnaire. www.sdqinfo.com
50. Achenbach T, Rescorla L: Manual for the ASEBA School-Age Forms & Profiles. Burlington, VT, University of Vermont, Research Center for Children, Youth, & Families, 2001
51. Ader DN: Developing the patient-reported outcomes measurement information system (PROMIS). Med Care 45:S1-S2, 2007
52. Health Measures. www.healthmeasures.net
53. Akshoomoff N, Newman E, Thompson WK, et al: The NIH Toolbox cognition battery: Results from a large normative developmental sample (PING). Neuropsychology 28:1-10, 2014
54. Alsalaheen B, Stockdale K, Pechumer D, et al: Validity of the immediate post concussion assessment and cognitive testing (ImPACT). Sports Med 46:1487-1501, 2016
55. ImPACT Applications, Inc. www.impacttest.com
56. Heitzer AM, Ashford JM, Harel BT, et al: Computerized assessment of cognitive impairment among children undergoing radiation therapy for medulloblastoma. J Neurooncol 141:403-411, 2019
57. Cogstate. www.cogstate.com
58. Macleod JW, Lawrence MA, McConnell MM, et al: Appraising the ANT: Psychometric and theoretical considerations of the Attention Network Test. Neuropsychology 24:637-651, 2010
59. Voress JK, Maddox T, Hammill DD: Developmental Assessment of Young Children (ed 2). Austin, TX, ProEd, 2012
60. Mullen EM: Mullen Scales of Early Learning. San Antonio, TX, Pearson, 1995
61. Sparrow SS, Cicchetti DV, Saulnier CA: Vineland Adaptive Behavior Scales (ed 3). San Antonio, TX, Pearson, 2016
62. Bruininks R, Woodcock R, Weatherman R, et al: Scales of Independent Behavior-Revised. Ithaca, IL, Riverside Publishing, 1996
63. Gioia GA, Espy KA, Isquith PK: Behavior Rating Executive Function—Preschool Version (BRIEF-P). Lutz, FL, Psychological Assessment Resource, 2001
64. Roth RM, Gioia GA, Isquith PK: Gioia GA Behavior Rating Inventory of Executive Function—Adult. PAR, 2005
65. Reynolds CR, Kamphaus RW: Behavior Assessment System for Children (BASC-3) (ed 3). Bloomington, MN, Pearson, 2015
66. Wechsler D, Hsiao-Pin C: WASI-II: Wechsler Abbreviated Scale of Intelligence. Pearson, 2011, pp 111-119
67. Wechsler D: Wechsler Intelligence Scale for Children (ed 5). Bloomington, MN, Pearson, 2014
68. Wechsler D: Preschool and Primary Scales of Intelligence (ed 4). San Antonio, TX, Pearson, 2012
69. Wechsler D: Wechsler Adult Intelligence Scales (ed 4). San Antonio, TX, Pearson, 2008
70. Adams W, Sheslow D: Wide Range Assessment of Visual Motor Abilities. San Antonio, TX, Pearson, 1995
71. Beery K, Buktenica N, Beery N: Beery-Buktenica Developmental Test of Visual Motor Integration (ed 6). San Antonio, TX, Pearson, 2010
72. Bracken B: Bracken Basic Concept Scale, Third Edition: Receptive. San Antonio, TX, Pearson, 2006
73. Wechsler D: Wechsler Individual Achievement Test (ed 3). San Antonio, TX, Pearson, 2009
74. Conners CK: Conners Kiddie Continuous Performance Test (ed 2). Cheektowaga, NY, MHS Assessments, 2015
75. Connors CK: Conners Continuous Performance Test (ed 3). Cheektowaga, NY, MHS Assessments, 2019
76. Manly T, Anderson V, Crawford J, et al: Test of Everyday Attention for Children (ed 2). San Antonio, TX, Pearson, 2016
77. Delis DC, Kaplan E, Kramer J: Delis-Kaplan Executive Function System. San Antonio, TX, Pearson, 2001
78. Korkman M, Kirk U, Kemp S: NEPSY (ed 2). San Antonio, TX, Pearson, 2007
79. Cohen M: Children’s Memory Scale. San Antonio, TX, Pearson, 1997
80. Wechsler D: Wechsler Memory Scale (ed 4). San Antonio, TX, Pearson, 2009
81. Delis DC, Kramer JH, Kaplan E, et al: California Verbal Learning Test (ed 3). San Antonio, TX, Pearson, 2017
82. Delis DC, Kramer JH, Kaplan E, et al: California Verbal Learning Test Children’s Version. San Antonio, TX, Pearson, 1994
83. Schmidt M: Rey Auditory Verbal Learning Test. Torrance, CA, WPS, 1996
84. Meyers JE, Meyers KR: Rey Complex Figure Test and Recognition Trial. Odessa, PAR, 1994
85. Sherman EMS, Brooks BL: Child and Adolescent Memory Profile. Lutz, FL, PAR, 2015

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Assessment and Monitoring of Neurocognitive Function in Pediatric Cancer

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Jurgen Lemiere
Employment: Covance

Melissa M. Hudson
Consulting or Advisory Role: Oncology Research Information Exchange Network, Princess Máxima Center

Sophie Thomas
Leadership: Dr Sophie Thomas Clinical Psychologist Ltd

No other potential conflicts of interest were reported.