Children's Oncology Group's 2023 Blueprint for Research: Behavioral Science

Leanne Embry[1], Kristin Bingen[2], Heather Conklin[3], Steven Hardy[4], Lisa Jacola[3], Jordan Marchak[5], Iris Paltin[6], Wendy Pelletier[7], and Katie Devine[8]

[1]The University of Texas Health Science Center at San Antonio Department of Pediatrics
[2]Medical College of Wisconsin Department of Pediatrics
[3]St Jude Children's Research Hospital
[4]The George Washington University School of Medicine and Health Sciences
[5]Children's Healthcare of Atlanta Inc Aflac Cancer and Blood Disorders Center
[6]The Children's Hospital of Philadelphia Department of Child and Adolescent Psychiatry and Behavioral Sciences
[7]University of Calgary Department of Oncology
[8]Rutgers Cancer Institute of New Jersey

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Abstract

As survival rates for childhood cancer have improved, there has been increasing focus on identifying and addressing adverse impacts of cancer and its treatment on children and their families during treatment and into survivorship. The Behavioral Science Committee (BSC) of the Children's Oncology Group (COG), comprised of psychologists, neuropsychologists, social workers, nurses, physicians, and clinical research associates, aims to improve the lives of children with cancer and their families through research and dissemination of empirically supported knowledge. Key achievements of the BSC include enhanced interprofessional collaboration through integration of liaisons into other key committees within COG, successful measurement of critical neurocognitive outcomes through standardized neurocognitive assessment strategies, contributions to evidence-based guidelines, and optimization of patient-reported outcome measurement. The collection of neurocognitive and behavioral data continues to be an essential function of the BSC, in the context of therapeutic trials that are modifying treatments to maximize event-free survival, minimize adverse outcomes, and optimize quality of life. In addition, through hypothesis-driven research and multi-disciplinary collaborations, the BSC will also begin to prioritize initiatives to expand the systematic collection of predictive factors (e.g., social determinants of health) and psychosocial outcomes, with overarching goals of addressing health inequities in cancer care and outcomes, and promoting evidence-based interventions to improve outcomes for all children, adolescents, and young adults with cancer.

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Leanne Embry, PhD, Department of Pediatrics, University of Texas Health Science Center at San Antonio, San Antonio, Texas

Kristin Bingen, PhD, Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI

Heather M. Conklin, PhD, Department of Psychology and Biobehavioral Sciences, St. Jude Children's Research Hospital, Memphis, TN

Steven Hardy, PhD, Division of Oncology, Children's National Hospital and Departments of Pediatrics and

Psychiatry & Behavioral Sciences, George Washington University School of Medicine and Health Sciences, Washington, DC

Lisa M. Jacola, PhD, ABPP-CN, Department of Psychology and Biobehavioral Sciences, St. Jude Children's Research Hospital, Memphis, TN

Jordan Gilleland Marchak, PhD, ABPP, Emory University School of Medicine and Aflac Cancer and Blood Disorders Center at Children's Healthcare of Atlanta, Atlanta, GA

Iris Paltin, PhD, ABPP-CN, Division of Oncology, The Children's Hospital of Philadelphia Department of Child and Adolescent Psychiatry and Behavioral Sciences, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

Wendy Pelletier MSW, RSW, Department of Oncology, Division of Psychosocial Oncology, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

Katie A. Devine, PhD, MPH, Department of Pediatrics, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ

Corresponding author:

Leanne Embry, PhD

Department of Pediatrics

University of Texas Health Science Center at San Antonio

San Antonio, Texas

Phone: 210-567-7481

Email: embryl@uthscsa.edu

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Abstract

As survival rates for childhood cancer have improved, there has been increasing focus on identifying and addressing adverse impacts of cancer and its treatment on children and their families during treatment and into survivorship. The Behavioral Science Committee (BSC) of the Children's Oncology Group (COG), comprised of psychologists, neuropsychologists, social workers, nurses, physicians, and clinical research associates, aims to improve the lives of children with cancer and their families through research and dissemination of empirically supported knowledge. Key achievements of the BSC include enhanced interprofessional collaboration through integration of liaisons into other key committees within COG, successful measurement of critical neurocognitive outcomes through standardized neurocognitive assessment strategies, contributions to evidence-based guidelines, and optimization of patient-reported outcome measurement. The collection of neurocognitive and behavioral data continues to be an essential function of the BSC, in the context of therapeutic trials that are modifying treatments to maximize event-free survival, minimize adverse outcomes, and optimize quality of life. In addition, through hypothesis-driven research and multi-disciplinary collaborations, the BSC will also begin to prioritize initiatives to expand the systematic collection of predictive factors (e.g., social determinants of health) and psychosocial outcomes, with overarching goals of addressing health inequities in cancer care and outcomes, and promoting evidence-based interventions to improve outcomes for all children, adolescents, and young adults with cancer.

Key Words : behavioral science, pediatric cancer, psychosocial, quality of life, supportive care, late effects

Background

Therapeutic advancements over the past 50 years have resulted in survival rates of over 80% for children diagnosed with cancer in the US.[1] Unfortunately, life-saving therapy is associated with adverse late effects that may impact survivors long after treatment ends.[2] For many children, treatment includes intensive regimens that disrupt typical psychosocial development and challenge the family system in unique ways. Distress among family caregivers often peaks at diagnosis and has garnered greater attention in the research literature over the past decade.[3] With improved survival outcomes, efforts to optimize quality of life (QOL), including neurocognitive, behavioral, and psychosocial outcomes, take on increased importance.

Although most children adapt well to diagnosis and treatment, vulnerable sub-groups remain. Children at highest risk for short- and long-term neurobehavioral problems are those with central nervous system (CNS) tumors, disease that requires CNS-targeted therapy, and children with pre-existing individual or familial risk factors.[4]Multiple social and psychological factors (e.g., race/ethnicity, socioeconomic status, family dynamics, trauma history, etc.) contribute to psychosocial outcomes and the trajectory of adaptation from diagnosis to survivorship.[5] Members of the Children's Oncology Group (COG) Behavioral Science Committee (BSC) are researchers and clinicians dedicated to examining the psychosocial impact of pediatric cancer and its treatment, during and after therapy, on children and their families.

Behavioral Science Committee

The mission of the BSC is to improve the lives and outcomes of children with cancer and their families through research and dissemination of empirically supported knowledge. The BSC recognizes that children with cancer and their families have unique needs requiring targeted scientific investigation and clinical implementation. The committee also seeks to educate professional and lay communities to promote better understanding and care of children with cancer and their families.

Comprised largely of psychologists and neuropsychologists, the BSC enjoys a diverse membership that includes social workers, nurses, physicians, and clinical research associates. These interdisciplinary collaborations, and the extensive training that psychologists and neuropsychologists receive in research design and outcome measurement, allow the BSC to lead and contribute meaningfully to the planning and conduct of QOL, behavioral and neurocognitive studies, and the development, implementation and dissemination of behavioral science interventions. Importantly, BSC members contribute perspectives of behavioral health researchers and clinicians who work with children with cancer, and their families, to discussions of COG practices including informed consent, return of research results, empirically supported interventions, and management of late effects. BSC members collaborate in empirical research within COG on behavioral science interventions that are both child- (pharmacological and/or behavioral) and systems-directed (family, school, health care providers).

COG offers advantages for conducting collaborative research in pediatric oncology. Examining behavioral science outcomes in the setting of clinical trials is essential to help determine the differential impact of new chemotherapy agents, varied treatment regimens, and therapy reduction on behavioral health outcomes. Because most pediatric cancers are rare, cooperative group research allows for large, diverse, and representative sample sizes to be statistically powered to answer research questions using homogeneous samples. It also provides the opportunity to examine risk and protective factors beyond what is possible in single institution studies.

Key Achievements

Liaison program

BSC representatives are appointed as liaisons and integrated into key steering committees of other Disease, Discipline, Domain, and Administrative Committees within COG (Table 1). This structure facilitates collaboration across committees and provides opportunities for BSC involvement in the earliest stages of new

concept development. The BSC emphasizes mentoring future generations of investigators via participation in the Young Investigators (YI) Committee mentorship program. The BSC appoints two representatives (YI paired with an experienced researcher) to every new study committee with behavioral science outcomes (e.g., neurocognitive, QOL, or patient-reported outcomes). BSC members included on study committees help refine research questions, provide rationale for inclusion of cognitive/QOL endpoints, and design assessment approaches. Table 2 summarizes BSC-relevant aims in active trials.

Neurocognitive Assessment Strategies

Historically, the BSC was primarily tasked with assessment and data collection in trials examining neurocognitive outcomes in response to treatment modifications. Our first concerted effort was the development of a free-standing protocol, ALTE07C1, designed to streamline and standardize neurocognitive data collection across COG trials. ALTE07C1 included a brief, direct assessment of cognitive domains commonly affected by cancer and its treatment and predictive of educational/occupational outcomes. A total of 945 children were enrolled on this protocol across COG trials over a span of 14 years, representing significantly improved data collection rates compared to prior COG trials. ALTE07C1 has been renamed the COG Standardized Neurocognitive Assessment Battery and is now embedded in relevant clinical trials.

After the development of ALTE07C1, BSC members began investigating the utility of a briefer, computerized assessment battery (Cogstate)[6] that can be administered without a psychologist or neuropsychologist. These computerized assessments have the potential to characterize neurocognitive functioning with less cost, time, practice effects, and patient burden than traditional measures. However, there are minimal data linking these measures to functional (educational/occupational) outcomes. With this in mind, BSC members obtained R01 grant funding to develop a comprehensive model of neurocognitive development in children with high-risk acute lymphoblastic leukemia to guide prediction of individual risk for cognitive declines and inform intervention development and timing. Relying on an early detection model of frequent neurocognitive monitoring, this initiative uses a multi-method approach of Cogstate (embedded in protocol AALL1131) and traditional measures (ALTE07C1) to understand neurocognitive function during and after treatment. Data collection is ongoing, and analysis is pending.

Evidence-based Guidelines

The BSC contributes to the development and endorsement of clinical practice guidelines to support behavioral health (e.g., mental, neurocognitive, psychosocial) across the cancer continuum from active treatment to long-term survivorship. To guide patient care during therapy, the COG Supportive Care Guidelines are a resource for up-to-date guidelines aligned with Institute of Medicine criteria[7] that are reviewed, evaluated, and endorsed by the COG Supportive Care Guidelines sub-Committee (https://www.childrensoncologygroup.org/cog-supportive-care-endorsed-guidelines). Currently, there are COG-endorsed guidelines to assist in the psychosocial management of fatigue[8] and chronic pain.[9] However, there remains a critical gap in supportive care clinical practice guidelines that meet current methodological standards.[10]

BSC members help to evaluate recent evidence on potential behavioral health late effects of treatment and generate recommended surveillance in the COG Long-Term Follow-Up Guidelines (http://www.survivorshipguidelines.org). These guidelines recommend annual assessment for educational and vocational progress, social functioning, mental health disorders, risky health behaviors, sleep, fatigue, and healthcare or insurance access for all long-term survivors. For patients with a history of exposure to neurotoxic therapy, guidelines recommend formal neuropsychological evaluation upon entry to survivorship care with repeated evaluations as needed for survivors with impairments in educational or vocational progress. Despite the wealth of observational data documenting neurocognitive and behavioral health late effects and associated risk factors, interventions to address these late effects of treatment are lacking and desperately needed to promote QOL among long-term survivors.[11–16]

Adolescents and Young Adults (AYAs)

AYAs, defined by the National Cancer Institute (NCI) as ages 15-39 years, are a vulnerable group in cancer care due to biologic and genetic differences, as well as risk factors that uniquely impact health and QOL outcomes, including concerns related to clinical trial access and enrollment, reproductive and sexual health, socioeconomic hardship, and mental health/psychosocial functioning.[17] Through BSC liaison work with COG's AYA Committee, cross-network collaboration with AYA investigators in medical oncology, and involvement in specific task forces, the BSC is poised to help address gaps in supportive care AYA research.

Given BSC expertise in QOL and patient-reported outcome (PRO) measurement, the BSC liaison was invited to join the National Clinical Trials Network (NCTN) AYA PRO Task Force formed in 2020. This task force yielded an AYA PRO core battery to assess health-related QOL and study-specific symptom burden, with recommended time points from study entry into survivorship.[18] Inclusion and evaluation of the implementation of this battery in AYA clinical trials is underway.

BSC members also have significant expertise in psychosocial development; thus, members are represented on the Sexual Health Task Force (SHTF) of COG'S AYA Committee. This task force aims to identify knowledge gaps and prioritize research questions to improve the quality of sexual health care for AYAs. The SHTF conducted a scoping review of sexual health among AYA cancer survivors that highlighted the post-treatment burden of sexual dysfunction and negative impact of cancer on romantic relationships and body image.[19] The SHTF also conducted a COG-wide survey of pediatric oncologists and advanced practice providers that suggested a need for provider education on AYA sexual health assessment, management, and communication.[20] Following the approach of the AYA PRO Task Force, the SHTF created a sexual health PRO battery with potential sexual health study endpoints for future inclusion in COG and cross-network trials. Future initiatives will focus on provider education and AYA patient-focused interventions to improve provider-patient sexual health communication and care.

Select Studies with BSC Involvement

Acute lymphoblastic leukemia (ALL)

ALL is the most common childhood malignancy; survival rates exceed 90%.[21,22] Treatment modifications have substantially reduced neurocognitive late effects, but survivors continue to demonstrate neurocognitive impairments secondary to disease and treatment that impacts educational/occupational outcomes.[23]

COG AALL1731 for children with newly diagnosed NCI standard-risk B-ALL, including children with Down syndrome and ALL (DS-ALL) examines whether treatment with blinatumomab in combination with chemotherapy lowers the risk for relapse and increases survival. AALL1731 includes embedded neurocognitive studies that will lay the groundwork for future risk-based neurocognitive screening and targeted interventions to improve survivors' QOL.

Recognizing the importance of the relationship between neurocognition and poverty,[24] AALL1731 includes the first comprehensive investigation of poverty-related neurocognitive outcome disparities in pediatric standard risk B-ALL. This embedded study explores whether children living in poverty (defined as presence of household material hardship – food, housing, or energy insecurity) at the time of diagnosis, are at risk for greater neurocognitive declines from baseline measured via Cogstate than their less impoverished counterparts. Additionally, among a subset of children enrolled in the household material hardship neurocognitive study, there is an aim investigating the impact of blinatumomab on caregiver burden and PROs. Finally, AALL1731 includes the first prospective study of neurocognitive outcomes in children with DS-ALL. Despite increased vulnerability to leukemia[25,26] and treatment toxicities,[27,28] these patients have been systematically excluded from decades of neurocognitive studies in childhood ALL[23] and thus very little is known about their neurocognitive outcomes. The DS-ALL neurocognitive study investigates individual, clinical, and socioenvironmental determinants of neurocognitive and QOL outcomes. Findings will drive the future inclusion of individuals with DS-ALL in evidence-based clinical practice guidelines for neurocognitive screening, survivorship care, and interventions.

Acute Promyelocytic Leukemia (APL)

APL is highly curable with existing therapies; therefore, there has been movement towards developing protocols that are less reliant on potentially cardiotoxic anthracycline chemotherapy. AAML1331 evaluated whether treating pediatric patients with APL using arsenic trioxide and all-trans retinoic acid would allow for a reduced or eliminated need for chemotherapy while maintaining high rates of event-free survival.[29] Environmental arsenic exposures confer serious risks to the developing brain[30,31] and, while arsenic trioxide is not thought to cross the blood-brain barrier, there have been reports of arsenic concentrations in the cerebrospinal fluid of patients treated with arsenic trioxide.[32,33]

Neurocognitive aims were included in protocol AAML1331. This study represented an important shift in approach that sought to demonstrate the feasibility of incorporating the neurocognitive assessment battery developed on ALTE07C1 into a therapeutic clinical trial rather than enrolling patients separately on the standalone ALTE07C1 protocol. The optional neurocognitive study was well-received by the AAML1331 study committee and participating COG sites, as patients were enrolled at 73 different institutions (86% of all AAML1331 sites). There was also strong interest from families, as the accrual target was reached early, and the study was granted special permission to over-enroll. Data collection is ongoing and, when complete, will clarify the short- and long-term safety of arsenic trioxide for the treatment of pediatric APL.

CNS Tumors

Children treated for brain tumors are at greatest cognitive risk given tumor mass effect and CNS-directed therapy.[34]Accordingly, many of the current trials emerging from the COG CNS committee center around modifying front-line therapy to maintain high survival rates (e.g., non-inferiority trials) while improving QOL. Since ALTE07C1 was discontinued as a free-standing protocol, there have been more than 10 new studies developed within the CNS committee that include cognitive and/or QOL assessments, highlighting the importance of collaborations with the BSC.

BSC members are also actively involved in intervention trials that seek to mitigate the emergence of cognitive late effects. ACCL2031 is a prime example whereby memantine, a glutamatergic NMDA receptor antagonist, is being investigated as a neuroprotectant in a randomized, placebo-controlled trial. Memantine has been shown to be neuroprotective in preclinical models[35,36] and resulted in less cognitive decline among adults receiving whole brain radiation therapy for brain metastases.[37] ACCL2031 randomizes children with primary CNS tumors, initiating cranial radiation therapy, to memantine or placebo. Change in cognitive functioning is the primary outcome for this trial. Cogstate and parent-reported executive function are required assessments for monitoring outcomes; the COG Standardized Neurocognitive Assessment Battery is recommended but not required. Trial enrollment is underway for this NCI-funded study. Notably, positive study findings would suggest cognitive late effects can be prophylactically ameliorated or even prevented.

Persistent Challenges

Like other Discipline Committees in the cooperative group, the BSC cannot develop and lead free-standing trials. Partnership with disease and domain committees is therefore critical to promote behavioral science aims early in concept development. There are logistical challenges to conducting behavioral science research in a cooperative group setting. As a more specialized discipline, some COG institutions do not have a BSC member to champion relevant studies at their site. In fact, some sites do not have ready access to psychology or neuropsychology, even for clinical services. Traditional assessments of neurocognitive function require a licensed psychologist/neuropsychologist for administration, prohibiting feasibility of this type of research in under-resourced institutions. In addition, some of the most psychometrically robust measures of neurocognition and QOL are copyrighted and have an associated cost, which can be burdensome at the institutional level; funding is not always available at the NCI level to help offset costs of materials or management of these data. There are often not resources to administer these measures in languages other than English, Spanish, or French, limiting our ability to meet the need of some vulnerable or marginalized populations.

Furthermore, behavioral science endpoints are often secondary or exploratory aims embedded in therapeutic trials, resulting in long waits for analysis, particularly when evaluating long-term follow-up. For example, if

a study aims to examine cognitive functioning at 5 years post-diagnosis, and the study accrues patients over a 5-year period, complete data for the behavioral science aim would not be available until 10 years after trial initiation. This can be a prohibitive timeline for investigators, especially YIs, who put significant effort into the planning and activation of a trial but must wait a long time for tangible products such as publications. This demonstrates the long time between research evidence and translation to routine care.

Strategic Plan: Opportunities and Future Directions

With significant improvements in cancer treatment, clinical trials have moved towards a precision medicine framework with scientific aims focused on optimizing QOL and minimizing toxicities while maintaining high survival rates. COG offers a unique collaborative environment to evaluate scientific aims with behavioral science outcomes in the context of large clinical trials with representative samples of children and AYAs with cancer from diverse racial, ethnic, and socioeconomic backgrounds. Aligned with our mission to improve outcomes for children with cancer and their families, the BSC is poised to contribute to the scientific advances of trials aiming to improve outcomes and promote evidence-based supportive care interventions to be translated into routine care.

Optimizing Patient-Reported Outcomes Data

Following the success of the AYA PRO Task Force[18], leaders from the BSC, Nursing, and Cancer Control committees are co-leading a new PRO Optimization Task Force to enhance the capacity and efficiency of patient- and caregiver-reported outcomes among youth <15 years of age. Valid measurement of PROs is essential to ongoing and future clinical trials focused on improving patient and family functioning during and after cancer treatment. There are many unique issues to consider for this age group, including the inclusion of multiple raters (e.g., child, caregiver, teacher) to account for developmental differences and functioning across settings and the wide range of cognitive, social, and emotional outcomes. This task force aims to develop a PRO battery to address the unique needs of children that is flexible to address study-specific aims. Other goals include expanding expertise within COG for the design and analysis of PRO endpoints, and developing infrastructure for optimal and efficient (i.e., electronic) capture of PRO data.

Prioritizing Social Determinants of Health (SDOH)

The BSC strongly supports ongoing work to identify and address health disparities in pediatric and AYA cancer care. In particular, the impact of household material hardship and adverse SDOH on pediatric oncology patients is well established in the literature.[38–40]

Although the gains achieved in cure rates in pediatric oncology may be attributed in large part to clinical trial organizations, children living in poverty and those identified as being from marginalized racial, ethnic, and minority groups are more likely to relapse and die at rates different from their non-Hispanic White counterparts.[41–44] Biology, tumor genetics, and response to initial therapy aside, pre-existing social and psychological factors, including SDOH, play a significant role in patient outcomes.[45,46]

Financial toxicity has been categorized as direct expenditures associated with treatment and access, and the indirect costs families sustain throughout the treatment trajectory related to loss of income and educational opportunities. Further, financial toxicity is detrimental to parental mental health and family functioning.[47–49]

Despite awareness of the multifaceted disparities and inequities in pediatric cancer, the systematic collection of information on SDOH and socioeconomic status has not been included in clinical trials.[50]Collaborative, multidisciplinary research studies within COG are beginning to embed these measures within clinical trials to better understand these factors and design interventions to ensure equitable access to, and benefit from, treatment.[51,52]

Recognizing Underserved Populations

The BSC has established two working groups within the committee to focus on underserved groups: AYA and Infants/Young Children. The AYA working group consists of nine BSC members with expertise in cognitive and psychosocial functioning in AYA Oncology. The primary objective is to generate behavioral

science-focused study concepts that are salient and impactful for the AYA cancer population that can be successfully implemented as large-scale, free-standing COG and cross-network trials. The Infants/Young Children working group consists of seven BSC members with expertise in the cognitive, social-emotional, and physical development of very young children. The primary objective is to generate recommendations for valid measurement of important outcomes for this group that can be feasibly implemented in the cooperative group setting, and to promote healthy development and preventative interventions for very young children and their caregivers.

Expanding BSC Involvement

The collection of neurocognitive and behavioral data in the context of clinical trials that are modifying treatment to minimize neurotoxicity continues to be paramount. The BSC will continue to work toward balancing the efficiency of computerized assessments with the more clinically relevant but time-intensive traditional, psychologist-administered measures of cognitive functioning. We will begin to address the exclusion of some marginalized populations from participation in cognitive outcomes research related to the lack of availability of testing materials in languages other than English, Spanish, and French. Relevant to cognitive outcomes, efforts are underway to examine the impact of anesthesia exposure over time, particularly in survivors of ALL. We will also be examining the impact of sensory deficits (i.e., vision/ hearing impairment) resulting from cancer or its treatment on cognitive outcomes and QOL.

There is a substantial breadth of expertise in the BSC that extends beyond neurocognitive functioning. Feasible interventions to address psychosocial and mental health late effects of treatment are lacking and desperately needed to promote QOL among long-term survivors of childhood cancer.[11–16] There is particular interest in dissemination and implementation science, including promoting the use of and adherence to evidence-based interventions. Studies are needed to examine how children with cancer perform at school – both academically and socially/emotionally – and what kinds of supports are required after treatment (e.g., 504/IEP, special education). Future research must focus on gathering data related to social attainment and its barriers, particularly among AYAs, including rates of graduation, employment, and independent living. Finally, there is interest in standardizing methods of distress screening and developing brief, feasible methods of reducing distress among patients of all ages and their families.

Conclusion

In the coming years, the BSC will prioritize initiatives focused on expanding the systematic collection of cognitive and psychosocial outcomes and predictive factors across trials, identifying and addressing health inequities in cancer care and outcomes, and promoting evidence-based interventions to improve outcomes for all children, AYAs, and their caregiver. The inclusion of behavioral science aims permits simultaneous evaluation of the neurocognitive and psychosocial impact associated with new advances in treatment. It also helps to expand the pool of COG investigators with expertise in behavioral science and PROs. Through collaborative efforts across COG, the BSC is well-positioned to improve the measurement of relevant outcomes, develop salient interventions, and begin addressing health disparities.

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TABLE OF ABBREVIATIONS

ALL	Acute lymphoblastic leukemia
APL	Acute promyelocytic leukemia
AYA	Adolescent and young adult
BSC	Behavioral Science Committee
CNS	Central nervous system
COG	Children's Oncology Group
CV	Carboplatin/vincristine
DS	Down syndrome
HSCT	Hematopoietic stem cell transplant
LGG	Low grade glioma
NCI	National Cancer Institute
NCTN	National Clinical Trials Network
NF1	Neurofibromatosis Type 1
PRO	Patient-reported outcomes
QOL	Quality of life
SDOH	Social determinants of health
SHTF	Sexual health task force
YI	Young investigators

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