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Resilience in the Time of COVID-19: Lessons Learned from an AYA Oncology Research Program

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2020 was a difficult year. Millions struggled with COVID-19 and its impact on personal, family, and society well-being. The Black Lives Matter movement (although not new in 2020) reminded us that systemic racism translates to perpetual health disparities and societal inequities. We experienced hurricanes, derechos, wildfires, and floods. The tension and animosity associated with the U.S. Presidential Election and its aftermath is palpable, ongoing, and profoundly polarizing.

And, as we in clinical oncology know: cancer still happened. Our patients received difficult news through face masks and video screens. They experienced changes in care delivery, with different chemotherapies, surgeries, and schedules than usual in order to keep patients and providers as safe as possible during the pandemic. They debated between fears of exposure to the SARS-CoV-2 virus in medical clinics and risking cancer relapse by staying away. They navigated the fear of dying from COVID-19 on top of the fear of dying from cancer.

Perhaps no group of patients with cancer has more psychosocial stressors than those diagnosed as adolescents and young adults (AYAs). These patients (defined by the National Cancer Institute as those 15 to 39 years old) are *also* navigating life stressors like developing autonomy and identity, education and vocational attainment, marriage, starting a family, parenting, caregiving, and—frankly—living. For these reasons, this group has high risks of poor psychosocial outcomes.¹ Compared to their peers, they are more likely to have ongoing mental health problems (including death by suicide), less likely to get married, less likely to

have a job, less likely to be paid as well if they have a job, less likely to have children, and more likely to have ongoing poor health-related quality of life.

With all that in mind, 2020 surprised me. 2020 was the year that confirmed my faith in AYA resilience.

I have been studying resilience for over a decade. When I started my career as a pediatric oncologist, I noticed the stressors of AYA patients and wondered if we were missing a critical opportunity: rather than wait for (and belatedly try to fix) poor outcomes, what would happen if we introduced concepts like resilience training to buffer the negative impacts of cancer and its treatments?

Over hundreds of hours of interviews with AYAs with cancer, we learned that their perceptions of resilience aligned with psychological theory: Resilience is a process of harnessing resources to sustain well-being in the face of adversity.² Those "resilience resources" tend to be the same in adversities as variable as cancer, natural disaster, poverty (and pandemics). They include three categories:

- Individual resources: personal characteristics and skills, community resources;
- Social support networks and communities; and
- Existential resources: the quest for meaning and purpose.

Which resources work best for whom and in which circumstances is variable, although once people identify their preferences, they tend to return to the same resources again and again. The most commonly endorsed AYA resilience resources included skills in stress-management, goal-setting, reframing negative thoughts, and benefit-finding.³ We translated each of these resources into a reproducible, bedside coaching program called "Promoting Resilience in Stress Management" (PRISM), and then tested PRISM in feasibility, acceptability,⁴ and phase 2 randomized clinical studies.⁵ Compared to AYAs who received usual oncology care, those who received PRISM reported higher self-perceived resilience, hope, and cancer-related quality of life, and lower psychological distress.^{5,6} At the start of 2020, we were busy testing PRISM in phase 3 clinical trials. When COVID-19 hit, the world (including our research) paused. We halted enrollment and waited for the return-to-normalcy. Perhaps like our very AYAs who realize only after the fact that life is not "on pause" and will never be the same after cancer, we quickly learned that our research plans would be irrevocably changed, too. It was time be research-resilient.

By the summer of 2020, we had converted PRISM to a virtual (Zoom-delivered) coaching program supported by a digital app. AYA patients loved it. "PRISM at my fingertips!" one exclaimed. Another commented on the "new normal" of Zoom. Seasoned coaching staff reported that patients seemed more—not less—engaged by video. "They always shared

what was hard, but now they seem to find comfort in the screen." We also noticed increased willingness and eagerness to practice resilience skills. "It seems pretty important these days," said one patient. Another said that gratitude came easier; being able to "stay in school" because the whole world had gone remote made cancer less lonely.

Now, in early 2021, I realize my patients taught me something: there is always change—sometimes hard, sometimes manageable. And there is always time—to heal, to learn, to adapt, and to grow. Resilience is not static, and it is not manifest by some sudden ability to thrive. Indeed, "getting through" (that time where we can only put one foot in front of the other) is a first, critical phase of resilience. Feeling uncertain, afraid, and exhausted is part of that phase, and all those feelings are normal. The second phase of resilience is when we begin to do the sometimes new and always deliberate work of "harnessing resources." Here, we acknowledge the hard, recognize what is in our control (and what is not), and lean into change. The last phase of resilience is when we "look back and learn." It is when we reflect, crystallize what we did, and recognize who we have become.

These phases are not linear; we constantly flow between and across them. While we are exhausted and "getting through," we may also start "harnessing resources" by considering what we have done in tough times before. We may also begin to consider how this adversity will change us. While we are deliberately "harnessing resources," we may start to identify new purpose by "looking back and learning."

The power of resilience is in its perpetual motion. Moving through and around these phases buffers us from the next adversity, whether we know it or not. It is a skill that can be refined and strengthened. Think of it this way: having cancer as an AYA is always hard, but there are moments when patients reflect and say, "I did that," and more, "now I know I can do something hard again." As we strengthen our metaphorical resilience muscle, we come to better understand our strengths, limitations, and opportunities for growth.

What does this mean for us now, in early 2021? Probably nothing but clarity. People have been navigating adversity for millennia. Although some seem to do it with more observable grace and skill than others, most keep going, despite their exhaustion. We have no choice but to be resilient. Today, after a year that changed the world, I have confidence and hope. We learned to be resilient in the time of COVID-19. We can, and will, be resilient again.

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A Focus On: Duloxetine to Prevent Oxaliplatin-Induced Neuropathy—A221805

By Mary R. Scott, MSN, RN, APN-BC, and Celia Bridges, BA, BSN

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Younger adults are being diagnosed more frequently with colorectal cancer (CRC). The American Cancer Society (ACS) reported a 51% increase in the incidence of CRC in adults <55 years from 1994 to 2014, and an 11% increase in mortality in the same age group from 2005 to 2015. Among the younger adults, highest incidence and mortality were in African Americans, Native Americans, and Alaska Natives.¹ Taking into account these data, in 2018 ACS updated its guidelines to recommend that adults aged ≥45 years (rather than 50) with average CRC risk undergo regular screening. The U.S. Multi-Society Task Force (USMSTF) on Colorectal Cancer also recommends that all average-risk African Americans initiate screening at age 45.² Earlier CRC screenings of younger adults, particularly young adults of color, will mean diagnosis at earlier stages of the disease and a consequent greater range of options for curative treatments.

However, one common and challenging side effect of earlier diagnosis/treatment for CRC is oxaliplatin-induced peripheral neuropathy (OIPN), which may be long-lasting or permanent and, in the case of younger patients, means the prospect of living with these conditions for many years. Patients with OIPN often experience numbness, tingling, and pain in their extremities, with severity ranging from mild to severe. Problems can vary from loss of ability to dress oneself and participate in hobbies to disabilities affecting mobility and/or occupation. Younger patients may be more severely impacted if they are unable to work, provide for their families, or reach life goals, all of which significantly affect quality of life. During oxaliplatin treatment, 85% of individuals experience OIPN severe enough to require dose modification,³ which may impact survival outcomes.

Prevention/reduction of the side-effect burden of potentially life-saving treatment, such as OIPN, is therefore an urgent priority. Current methods for addressing the serious, debilitating side effects of OIPN are limited to dose reduction/delay or stopping treatment altogether, all of which compromise the efficacy of treatment. Duloxetine has demonstrated effectiveness in the treatment of OIPN, including reduction of associated chronic pain),⁴ and for multiple painful conditions including diabetic neuropathy and fibromyalgia. Pre-clinical trials in animals have also demonstrated duloxetine's effectiveness in preventing OIPN.

In May 2020, the Alliance for Clinical Trials in Oncology opened research study <u>A221805—Duloxetine to Prevent Oxaliplatin-induced Chemotherapy-induced Peripheral Neuropathy—led by principal investigator Ellen M. Lavoie Smith, PhD, MSN, RN, AOCN®, FAAN. This randomized, double-blinded, placebo-controlled clinical trial is testing the effectiveness of duloxetine in preventing the potentially chronic and disabling side effects of OIPN. Participants are adults with Stage II or low-risk Stage III colorectal cancer who will undergo surgery followed by 3 months of oxaliplatin-based adjuvant chemotherapy (CAPOX 4 cycles or FOLFOX 6 cycles), a mainstay treatment for CRC that causes acute and persistent oxaliplatin-induced peripheral neuropathy.</u>

A221805 is a phase 2 to phase 3 trial designed to determine if one of two duloxetine doses (30 mg or 60 mg), when compared to placebo, might prevent OIPN (phase 2. If duloxetine appears to be more effective than placebo in the phase 2 trial, the most promising dose (30 mg or 60 mg) will be compared to placebo (phase 3) to assess duloxetine's effectiveness for preventing OIPN sensory symptoms and chronic neuropathic pain. Study drug is taken from start of chemotherapy treatment to one month after chemotherapy completion, followed by one week of tapering off the drug. Patients are followed for 18 months to measure both acute and chronic symptoms.

Duloxetine's safety profile has been extensively studied in those with fibromyalgia, depression, and musculoskeletal pain. Because of an FDA black box warning about an increased risk of suicidal thinking/behavior in children, adolescents, and young adults, patients under the age of 25 are not eligible for this study. Other cautions include a risk of increased bleeding and a note to avoid ingestion of alcohol. Potential drug interactions may occur with CYP1A2 or CYP2D6 inhibitors, so they should be avoided.

Neuropathy symptoms, including numbness, tingling, and pain, are most accurately described by those who experience them—the patients. Therefore, patient-reported outcome (PRO) surveys were incorporated into this study as a critically important component of data collection. Because the sensory symptoms of OIPN can be both acute and chronic, PRO surveys are used for serial measurement of symptoms for 18 months after oxaliplatin treatment. To facilitate the use of PROs, participants are offered and encouraged to utilize the iMedidata Rave Patient Cloud ePRO App on a smartphone or tablet for electronic (ePRO) surveys, which participants can easily complete on their device in a variety of settings. This

free app reminds participants when their surveys are due, and securely sends responses directly to the database. Paper booklets are available for participants who do not have the necessary electronic device or WiFi access.

A primary objective of A221805 is to determine the effectiveness of duloxetine to prevent OIPN sensory symptoms and chronic neuropathic pain. Currently the only methods of addressing these symptoms are oxaliplatin dose reduction/delay or treatment cessation; however, these interventions compromise treatment efficacy. If duloxetine is found to be effective in mitigating these symptoms, the benefits would be two-fold: 1) dose reductions/delays or treatment cessation may be avoided, thereby improving treatment efficacy, and 2) the burden of long-term side effects of OIPN, including disability and diminished quality of life, could be lightened.

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Clinical Trials and AYAs: Listening and Learning

By Krista Nelson, MSW, LCSW, OSW-C, BCD

Krista Nelson is Program Manager Quality and Research, Cancer Support Services and Compassion, Providence Cancer Institute in Portland, Oregon. She defines her role as providing support for people and their families throughout the cancer continuum and sharing the expertise that she has learned from other patients with cancer. She facilitates a Young Survival Coalition online support group for women with metastatic cancer and runs a program for children with a parent with cancer. Ms. Nelson is ACCC President Elect.

Understanding and responding to the needs of adolescent and young adult (AYA) patients with cancer requires a willingness to look at each person as an individual and meet them where they are. This is the core of all quality care. Just as we talk about precision anticancer treatment, I believe we need to consider precision psychosocial care.

The National Cancer Institute defines AYA patients as between the ages of 15 and 39. This covers a wide span of chronological age as well as life stage, circumstances, achievements, and aspirations. Diversity defines this population—while some 29 year olds will have more in common with those in their early 20's, others will feel more connected to those in their late 30's.

One thing that AYAs often *do* have in common, regardless of age, is the feeling that they are not getting all the information they need, or the "whole story." A recent example of this came up during a support group for women under age 40 with Stage IV breast cancer that I facilitate. I was explaining palliative care and a participant asked, "Why are the doctors keeping palliative care from me?" The patient felt she would benefit from this information, while the physician's perspective was, "I don't want the patient to think I've given up hope." Through facilitated peer group support, not only can AYA patients connect with others at similar stages in life, but also the patient's voice can help us to better understand unmet needs.

When speaking with new residents and nurses about AYA patients, I recommend that in meeting with patients under age 40, at a minimum, they discuss:

- Fertility—Just as AYAs deserve an expert in cancer care, they also deserve an expert in fertility care. Be prepared to provide patients with referral information.
- Peer support—Have information and resources to support AYAs and connect them with others in a similar life situation.
- Decision makers—AYAs may be in non-traditional relationships. If there is a crisis who will their decision maker be?

Engaging with AYA patients requires flexibility, openness, and a willingness to be innovative. At Providence Cancer Institute, I specialize in working with children who have a parent with cancer. It's believed that 24% of patients getting treatment for cancer have kids aged 18 or younger at home. That is one-quarter of our patient population. When physicians are talking to these patients about their treatment options, how many may be thinking: "How am I going to pay my rent? How am I going to tell my kids? What about my job?" Engaging psychosocial support along the cancer care continuum helps identify barriers, as does rescreening for distress when there is a change in care.

Time pressures, finances, and life responsibilities are known barriers to clinical trial participation for AYAs. Any time we ask a patient to do something more that requires time away from work, there is potential financial impact. One thing we do not do well with in cancer care is being flexible with our treatment options. In presenting on building and improving quality psychosocial care for AYA patients, Karen Fasciano, PsyD, Senior Psychologist and Young Adult Program Director at the Dana-Farber Cancer Institute, has stressed the importance of innovation and engagement for this patient population.

This is especially the case with clinical trials, which are by nature rigid. With the AYA population in particular, but for others as well, non-traditional jobs may mean that to participate they need a little different schedule or more flexibility. When you're asking someone to come in weekly to get blood draws, that impacts their finances. Making clinical trials more accessible for AYAs (and others) requires stepping back from the protocol and asking: Is there a way to add a little more flexibility so that participation in the study would be feasible for AYA patients?

At my cancer center, research nurses are heavily involved in clinical trial recruitment. A physician may present the trial option to the patient, but the research nurse explains all the ins and outs of the study. With this approach, patients feel like they have more time to ask questions and get answers.

Another step we've taken is to include young adults on our cancer center's patient advisory board. This empowers AYAs to share their lived experience of care at our institution, allowing us to listen and learn.

Finally, a strategy cancer programs may want to consider is developing an AYA patient navigator position. This would not be a volunteer role— with training, it could be a position for a former patient or peer supporter who has been through cancer treatment and may have participated in a clinical trial.

Resources

Davis LE, Janeway KA, Weiss AR, et al. <u>Clinical trial enrollment of adolescents and young adults with sarcoma</u>. *Cancer*. 2017;123(18):343-3440. This commentary that lays out needed changes to realize increased enrollment of AYAs in sarcoma clinical trials.

Freyer DR, Seibel NL. The clinical trials gap for adolescents and young adults with cancer: recent progress and conceptual framework for continued research. Curr Pediatr Rep. 2015;3(2):137-145. This article includes a Clinical Trial Pathway to Enrollment. Each step in the pathway is multi-faceted. In conclusion, the authors write the path starts with "having clinical trials focused on cancers relevant to this age group that are available, accessible, effectively presented, and ultimately acceptable to an eligible patient. Addressing all of these will require continued research in areas as diverse as cancer biology and therapeutic decision-making, involving institutions ranging from NCI to community-based hospitals."

Isack A, Santana VM, Russo C, Klosky JL, Fasciano K, et al. <u>Communication regarding therapeutic</u> <u>clinical trial enrollment between oncologists and adolescents and young adults with cancer</u>. *J Adolesc Young Adult Oncol*. 2020 Oct;9(5):608-612. Authors surveyed 193 AYA patients and reviewed medical records of informed consent discussions. Survey results showed that many respondents were unable to "accurately report" if they'd been offered a clinical trial. Of respondents on clinical trials, more than

one-quarter did not recall being enrolled. Authors offer several suggestions for approaching clinical trial conversations with AYAs.

National Cancer Policy Forum. Board on Health Care Services; A Livestrong and Institute of Medicine Workshop; Institute of Medicine. <u>Identifying and Addressing the Needs of Adolescents and Young Adults with Cancer.</u> 2014. National Academies Press: Washington, DC.

Roth M, Mittal N, Saha A, Freyer DR. <u>The Children's Oncology Group Adolescent and Young Adult Responsible Investigator Network: A New Model for Addressing Site-Level Factors Impacting Clinical Trial Enrollment.</u> *J Adolesc Young Adult Oncol.* 2020;9(4):522-527. This report outlines multiple site-level barriers to AYA clinical trial enrollment identified by the COG AYA Responsible Investigator Network and describes a novel model for developing and integrating solutions via a nationally coordinated strategy. Site-level barriers fell into four main areas: lack of available trial; poor communication between pediatric and medical oncology; logistical barriers to access; and need for leadership support.

Smith AW, Keegan T, Hamilton A, et al. <u>Understanding care and outcomes in adolescents and young adults with cancer: A review of the AYA HOPE study</u>. *Pediatr Blood Cancer*. 2018;Oct 7: e27486. This review of the 10-year NCI-supported AYA Hope Study that recruited patients diagnosed at ages 15 to 39 with germ cell, Hodgkin and non-Hodgkin lymphoma, acute lymphoblastic leukemia, and sarcoma from SEER cancer registries into the first multicenter U.S. population-based study of medical care, physical, and mental health outcomes for AYAs with cancer. The authors write: "Review of the 17 published manuscripts showed low awareness of clinical trials and substantial impact of cancer on financial burden, education and work, relationships and family planning, and physical and mental health. It highlights the feasibility of a longitudinal population-based study and key lessons learned for research on AYAs with cancer in and beyond the United States."

ACCC Webcast: COVID-19 Implications for Cancer Clinical Research and Quality Care

The COVID-19 pandemic has thrown a wrench into every corner of the American healthcare system, and clinical research is no exception. In light of physical distancing and public safety recommendations, research programs have made significant adjustments, including virtual approaches to site selection and data collection and increased use of telehealth services. On Wednesday, February 10, join a discussion on the impact of COVID-19 on cancer research protocols and patients' experiences. An expert panel of past ACCC Presidents will share perspectives on changes to clinical research during the pandemic, review available guidance, and look at how current adaptations can be made more sustainable in post-pandemic research. Click here to register.

Outcomes & Survivorship Research: An Interview with Smita Bhatia, MD, MPH

9 ACCC Research Review: February 2021

Smita Bhatia, MD, MPH, is the Director of the Institute for Cancer Outcomes and Survivorship at the University of Alabama (UAB) School of Medicine. She holds professorship in the Division of Pediatric Oncology and serves as the Vice Chair for Outcomes Research in the Department of Pediatrics.

An internationally renowned leader in cancer survivorship and outcomes research and the author of more than 320 publications, Dr. Bhatia has received continual funding from the National Institutes of Health and the Leukemia & Lymphoma Society since 2000. Her research encompasses the study of the burden of morbidity experienced by patients with cancer across the entire age spectrum; an understanding of etiology and pathogenesis of the long-term complications identified in cancer survivors; development of risk prediction models to identify survivors at the highest risk; and intervention trials to reduce the complications among cancer survivors.

ACCC Research Review interviewed Dr. Bhatia via email for her perspective on how her research interests have evolved and the current research needs related to outcomes and survivorship of AYA patients with cancer.

ACCC: As an international leader in research on cancer outcomes and survivorship, can you share a little about how your research interests have evolved over the past decade? What drives your passion for this work?

Dr. Bhatia: My research interests have evolved from making observations about the long-term outcomes in cancer survivors, to now attempting to understand the role of genetics in helping us understand which groups of survivors are at highest risk, and then developing targeted interventions to reduce the morbidity in this population. My overarching goal is to improve the quality and quantity of life of cancer survivors from all walks of life.

ACCC: The Institute for Cancer Outcomes and Survivorship at UAB conducts research on the long-term health and well-being of cancer survivors across all cancer types and ages. Thinking specifically of the AYA patient population, what do you see as critical unmet needs in terms of research on late and long-term effects of cancer treatment?

Dr. Bhatia: The late and long-term effects of cancer treatment in AYA cancer survivors have not been examined. Thus, we do not have any evidence to support the needs of our survivors of AYA cancers.

ACCC: So, to put in simple terms, there is a compelling need for more research on late and long-term effects of cancer in the AYA patient population?

Dr. Bhatia: Yes. There is a critical need to understand the burden of long-term morbidity—physical and psychosocial—carried by the AYA patient population.

ACCC: How is the increased use of targeted therapies, immune checkpoint inhibitor therapies, and the introduction of CAR-T therapy impacting cancer outcomes and survivorship research?

Dr. Bhatia: Immune checkpoint inhibitors and CAR-T cell therapies are a recent addition to the therapeutic armamentarium for childhood cancer. These patients will need to be followed for a few more years before we can describe the long-term outcomes in this population.

We are embarking on a study to examine the long-term outcomes after CAR-T cell therapy in a multi-institutional setting.

ACCC: Are there some specific studies from UAB related to the AYA patient population that you would like to highlight?

Dr. Bhatia: Two recent papers focus on acute lymphoblastic leukemia in AYA patients:

- Wolfson JA, Richman JS, Sun C-L, Landier W, et al. Causes of inferior outcome in adolescents and young adults with acute lymphoblastic leukemia: across oncology services and regardless of clinical trial enrollment. *Cancer Epidemiol Biomarkers Prev.* 2018 Oct;27(10):1133-1141. Doi: 10.1158/1055-9965.EPI-18-0430. Epub 2018 Sep 27. Available online at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6238217.
- Wolfson JA, Bhatia S, Ginsberg J, Becker LK, et al. Expenditures among young adults with acute lymphoblastic leukemia by site of care. *Cancer*. 2021; Jan 19. doi: 10.1002/cncr.33413.
 Online ahead of print. Available online at: https://acsjournals.onlinelibrary.wiley.com/doi/abs/10.1002/cncr.33413.

ACCC: What should community cancer care providers (MDs, NPs, APPs, RNs, pharmacists, etc.) know about the findings/resources from the Childhood Cancer Survivorship Study (CCSS) as these relate to the AYA patient population?

Dr. Bhatia: Some recent publications from the Kaiser Health System address this:

- Armenian SH, Xu L, Cannavale KL, Wong FL, et al. Cause-specific mortality in survivors of adolescent and young adult cancer. *Cancer*. 2020;126(10):2305-2316. doi: 10.1002/cncr.32775.
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- Tanenbaum HC, Wolfson J, Xu L, Hahn EE, et al. Adherence to cardiomyopathy screening guidelines among adolescent and young adult cancer survivors exposed to chest radiation and/or anthracyclines. *J Cancer Surviv*. 2020;Nov 10. doi: 10.1007/s11764-020-00965-w. Online ahead of print. Available online at: https://pubmed.ncbi.nlm.nih.gov/33170480/.

ACCC: You've mentioned the need for "intermediate markers of health" in cancer survivors that may signal early disease and provide opportunities for intervention. Can you say more about the promising research in this area?

Dr. Bhatia: Intermediate markers of health or biomarkers are necessary to determine the efficacy of an intervention within a more reasonable timeframe, as the actual long-term effects take many years to develop.

ACCC: What specific resources would you recommend for community-based cancer clinicians caring for AYA cancer survivors?

Dr. Bhatia: I would recommend that they follow the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers Version 5.0, available on its website, and the NCCN Adolescent and Young Adult (AYA) Oncology Guidelines (login required).

ACCC: What is on the horizon in terms of the ability to stratify AYA patients for high risk for late effects of treatment and evidence-based interventions to reduce this risk?

Dr. Bhatia: There are several groups in the country who are undertaking detailed evaluation of the burden of morbidity carried by AYA cancer survivors. The next step here would be to develop risk prediction models, and then develop and test targeted interventions to reduce the morbidity.

ACCC: Despite progress, disparities in the burden of cancer and access to care persist. For example, the recent AACR Cancer Disparities Progress Report 2020, states that Hispanic children are more than 50% less likely to enroll in clinical trials testing treatments than non-Hispanic White children. What is the most pressing issue in terms disparities in outcomes and survivorship among AYA cancer survivors?



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