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Disparities in Pediatric Oncology: The 21st Century Opportunity to Improve Outcomes for Children and Adolescents With Cancer

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Abstract

Adult cancer disparities have been documented for decades and continue to persist despite clinical advancements in cancer prevention, detection, and treatment. Pediatric cancer survival has improved significantly in the United States for the past 5 decades to over 80%; however, disparate outcomes among children and adolescents with cancer still affect many populations in the United States and globally, including racial and ethnic minorities, populations with low socioeconomic status, and residents of underserved areas. To achieve equitable outcomes for all children and adolescents with cancer, it is imperative that concerted multilevel approaches be carried out to understand and address health disparities and to ensure access to high-quality cancer care. Addressing social determinants of health, such as removing barriers to health care access and ensuring access to social supports, can reduce pediatric cancer disparities. Nevertheless, public health policy, health system interventions, and innovative delivery of evidence-based services are

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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critically needed. Partnerships among patients, caregivers, and health care providers, and among health care, academic, and governmental institutions, have a pivotal role in reducing cancer disparities and improving outcomes in the 21st century.

INTRODUCTION

In the United States, childhood and adolescent cancer is the leading cause of death by disease past infancy, with more than 17,000 children and adolescents younger than age 21 diagnosed annually.[1] Overall survival (OS) has improved tremendously over the past 5 decades,[2] and today, over 80% of U.S. children with cancer will be long-term survivors. These improvements have been driven in large part by multicenter clinical trials conducted by national and international cooperative groups to improve risk stratification, treatment intensity, and supportive care.[3] Despite this highly standardized approach to research and care delivery, underserved children, including those from racial and ethnic minority groups and/or of lower socioeconomic status, experience higher rates of relapse, decreased OS, and inferior psychosocial outcomes compared with their non-Hispanic White or wealthier counterparts.

Although national guidelines[4,5] call for elimination of cancer disparities, research to understand mechanisms driving inferior outcomes for underserved children with cancer is lacking, and few evidence-based interventions to address these disparities have been developed. The pursuit of health equity in pediatric oncology represents an opportunity in this unique political moment when unprecedented attention is being paid to racial and social justice. Moreover, as outcomes for the overall pediatric population with cancer continue to improve, targeting efforts to those who experience persistent inferior outcomes is the best approach to ensure equitable gains in reducing morbidity and mortality. Similar to current approaches to identify patients with high-risk disease characteristics and to allocate more intensive therapy to these patients, it is imperative that underserved patients at risk for inferior outcomes also be identified and their risk be mitigated through targeted interventions.

The National Cancer Institute defines cancer health disparities as adverse differences in cancer incidence, prevalence, burden, mortality, and survivorship that exist among specific U.S. populations.[4] Racial/ethnic and sex/gender disparities are the most frequently studied; however, other factors such as income, education, health insurance coverage, distance to health care facility, cultural dynamics, English proficiency, and health literacy have been found to be relevant as well.[5] For some specific groups, such as gender minorities, the lack of available data makes it difficult to even assess disparities.[6] Underserved populations in low- and middle-income countries are also greatly impacted by health disparities.[7] The worldwide COVID-19 pandemic has laid bare systemic and long-standing inequities and has disrupted access to health care services; these disruptions disproportionately affect those already facing health disparities within our health care delivery system, making tackling these issues critical.[6]

Black children have consistently experienced worse OS across pediatric cancer diagnoses. In fact, these racial disparities have recently widened for acute myeloid leukemia and

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neuroblastoma.[8] Hispanic children have a much higher incidence of several cancers, such as leukemia and lymphoma, and poorer 5-year OS than their non-Hispanic White counterparts (74% vs. 81%, respectively).[9-11] The pervasive and escalating nature of these disparities suggests that the underlying mechanisms driving survival disparities across disease groups relate to more complex factors than solely tumor biology,[2,8-10] which certainly varies by type of cancer.

This brief review highlights key disparities along the cancer continuum from access to care through cancer-directed therapy, including enrollment in clinical trials, and summarizes the complex landscape that influences achievement of equitable clinical outcomes for all children with cancer within the United States and globally.

Pediatric Cancer Disparities: Scope of the Problem at the Population-Based Level

ASCO's policy statement on cancer disparities and health equity emphasizes the importance of examining how multiple dimensions of patients' identities intersect to affect health outcomes,[6] including race, ethnicity, and insurance status. Cancer registries present an opportunity to evaluate disparities at the population-based level. These data are essential for generalizability to the broader population in the setting of known disparities in access to specialized cancer centers and disparities in enrollment into clinical trials.[12-14] However, there are also limitations to these data, in that they frequently lack clinical details relevant to prognosis and outcomes, including disease biology and treatment information (Table 1).

Race and ethnicity are social categories constructed based on socioeconomic and political forces and are an imperfect proxy, at best, for genetic ancestry. As oncologists, a considerable proportion of risk stratification and prognosis is based on cancer genomics, and thus, it is tempting to use race as a biologic guidepost for genetic differences among our patients.[15] However, there is mounting evidence that race is not a reliable proxy for genetic differences or the relation between ancestry[16] and genetics. At the very least, we must accept that racial/ethnic groups represent genetically heterogeneous populations that lack clear-cut genetic boundaries.

Racial and Ethnic Disparities

Using the National Cancer Institute's Surveillance, Epidemiology, and End Results database, Kahn et al[17] described notable disparities in survival trends of pediatric and adolescent/young adult patients (defined as age 15 to 39) with hematologic malignancies, including acute lymphoblastic leukemia, acute myeloid leukemia, and Hodgkin lymphoma, over a 4-decade period. Focusing on their data from 2004 to 2007, in acute lymphoblastic leukemia, Hispanic children had worse survival (88% for Hispanic children [95% CI, 85–91] vs. 93% for non-Hispanic White children [95% CI, 91–95]).[17] Among Black children with acute myeloid leukemia, worse survival was observed (54% for Black children [95% CI, 34–70] vs. 71% for non-Hispanic White children [95% CI, 61–79]).[17] In Hodgkin lymphoma, worse outcomes were observed in Black adolescent/young adult patients (92% for Black adolescent/young adults [95% CI, 88–95] vs. 96% for non-Hispanic White adolescent/young adults [95%CI, 95–97]).[17] Care for adolescent/young adult patients with leukemia and brain tumors at specialized cancer centers has been shown to mitigate disparities

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between adolescent/young adult patients and their younger counterparts[18,19]; however, it is unclear the effect that treatment at such centers similarly has upon racial and ethnic disparities. The Surveillance, Epidemiology, and End Results database was also used to describe survival disparities for common pediatric extracranial solid tumors between 1985 and 2005.[20] Overall, Black and Asian/Pacific Islander children had a higher risk of death compared with non-Hispanic White children (HR, 1.31, and HR, 1.34, respectively; $p < .05$). Black children had a higher risk of death from germ cell tumors, hepatoblastoma, and nonrhabdomyosarcoma soft tissue sarcomas. Interestingly, differences in survival between Hispanic and non-Hispanic children were not observed. For brain tumors, a recent study demonstrated that Hispanic and Black children had substantially higher hazard of death than non-Hispanic White children (Hispanic: HR, 1.25; 95% CI, 1.18–1.31; Black: HR, 1.12; 95% CI, 1.04–1.21).[21] These differences were most prominent among those with high-grade tumors, with no difference observed in diffuse astrocytoma. In a study using the California Cancer Registry to investigate disparities among children with high-grade gliomas, Hispanic children had worse survival than non-Hispanic White children (HR, 1.62; 95% CI, 1.24–2.11).[22]

Health Insurance–Based Disparities

In the United States, health insurance coverage has consistently been demonstrated to be one of the strongest predictors of cancer outcomes.[6,7] Health insurance is often used as a proxy for household income, as child eligibility for public insurance (e.g., Medicaid) is based on state-defined income thresholds. The Patient Protection and Affordable Care Act, enacted in 2010, requires Medicaid coverage for all children up to 133% of the federal poverty line.[23] The 1997 Children's Health Insurance Program was created to subsidize health insurance for children[24] in working families with incomes too high to qualify for Medicaid. In 13 states, the income eligibility threshold for the Children's Health Insurance Program is up to 400% of the federal poverty line.[25] Medicaid and the Children's Health Insurance Program cover more than one in three (37%) of children overall, and over half of Hispanic (52%) and Black children (54%). Among children with cancer, similar differences are observed, with Black children being more likely to have public insurance than non-Hispanic White children (73% vs. 37%).[8] The complementary coverage of these two programs has led to relatively few uninsured children (less than 7%).[23]

Health insurance is also used as a measure of health care access, given that the ability to pay for health services or have them covered is a determinant of the care sought and received.[24] In pediatrics, disruptions in health insurance coverage are associated with reduced access to care.[26] Among adult patients with cancer, a review found that those with disruptions were more likely to present at an advanced stage (odds ratio, 1.2–3.8) and have worse survival (HR, 1.28–2.43) compared with patients without insurance disruptions.[27]

Based on the existing U.S. insurance infrastructure, the adolescent/young adult population is at particular risk for insurance disruptions and is especially vulnerable to the impact of health insurance on health outcomes. In a population of 66,556 patients with cancer in the Surveillance, Epidemiology, and End Results database between 2007 and 2014, noteworthy survival disparities were associated with health insurance status in adolescents with acute

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lymphoblastic leukemia, acute myeloid leukemia, and Hodgkin lymphoma.[28] Public or no insurance increased the risk of death, and this effect increased with age for most cancer types.

In an attempt to disentangle insurance as a measure of access to care from insurance as a proxy for low-income status, Keegan et al[29] distinguished adolescent/young adult patients with continuous Medicaid coverage prior to diagnosis compared with those who obtained Medicaid coverage at diagnosis using a linkage between the California Cancer Registry with Medicaid enrollment files. Patients with Medicaid insurance had significantly worse survival regardless of when coverage began (Medicaid at diagnosis: HR, 1.51; 95% CI, 1.42–1.61; continuous Medicaid: HR, 1.42; 95% CI, 1.33–1.52; and discontinuous Medicaid: HR, 1.64; 95% CI, 1.49–1.80). Notably, adolescent/young adults who enrolled in Medicaid at diagnosis (and were uninsured prior to diagnosis) were 2.2 to 2.5 times more likely to be diagnosed with later-stage disease (vs. Medicaid discontinuously enrolled, 1.7 to 1.9 times, and Medicaid continuously enrolled, 1.4 to 1.5 times) compared with those with private insurance.[29] These findings suggest that access to care figures prominently into the impact of health insurance, given that all three study populations qualify for Medicaid based on income.

For patients with acute myeloid leukemia in the Pediatric Health Information System administrative database, the joint effect of Black race and public insurance on induction mortality (HR, 3.91; 95% CI, 1.32–11.6) was greater than expected based on the independent effects, suggesting that the absolute difference between Black and non-Hispanic White patients is larger among publicly insured children.[30]

Taken together, population-based data demonstrate that racial and ethnic minority children and adolescents, and those of lower socioeconomic status, experience consistent disparities in cancer presentation and survival outcomes across diseases.

Minority Underrepresentation in Cancer Research

The National Institutes of Health Revitalization Act of 1993 mandated the inclusion of women and minority populations in clinical trials.[31] However, to date, only 2% of approximately 10,000 National Cancer Institute clinical trials have representative minority participants.[32] By 2060, Hispanic children will comprise 33% of the U.S. childhood population.[33,34] Despite this growth and the National Cancer Institute's efforts to include minority individuals in research,[35] Hispanic and Black adults are severely underrepresented in research participation compared with non-Hispanic White adults (1% to 7% vs. 15% and 67%, respectively).[36] Participation rates in adult cancer clinical trials are even lower, at 0.4% to 2.2% for Hispanic patients and 5.4% for Black patients,[37] even at National Cancer Institute–designated comprehensive cancer centers.[38] In addition, data show that Black and Hispanic adolescent/young adults with acute lymphoblastic leukemia are less likely to be treated at National Cancer Institute–designated comprehensive cancer centers or sites affiliated with the Children's Oncology Group.[19] These patterns of decreased enrollment of patients from minority groups have also been observed in pediatric cancer clinical trials,[39] with Hispanic children being reported as underrepresented in pediatric cancer research.[40]

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Lower survival rates observed at the population level are at least partially attributable to lower enrollment in clinical trials.[41]

Differences between participants in clinical trials and real-world populations, who ultimately will receive the treatments once they become standard of care, preclude the generalizability of results and equitable translation and assessment of treatment benefits for underrepresented minority groups. Nonrepresentative trial participation in a field that is centered on trial-based cancer discovery perpetuates existing disparities by precluding the ability to assess pharmacogenomics characteristics in metabolism and toxicity in minority populations, which is highly relevant to real-world utilization of cancer-directed therapies. Similarly, patient-level predictors of adherence to complex therapies cannot be evaluated if diverse populations are not represented in clinical trials.

Clinical Trial Participation Inequity in Adolescents With Cancer

Survival disparities among adolescents (age 15 to 21) persist despite overall improvement in survival, morbidity, and quality of life for younger children with cancer in the United States.[42] Evidence shows that participation in clinical trials is associated with better survival outcomes among children and adolescents with cancer;[2,39] however, adolescents have lower clinical trial participation rates compared with younger age cohorts (30% vs. 68%, respectively).[28,38,40] Globally, adolescent enrollment rates into cancer clinical trials are the lowest of any age group.[2] Poor enrollment of adolescents into cancer clinical trials may contribute to inferior survival gains compared with children, beyond differences in tumor biology. For example, in acute lymphoblastic leukemia, the most common pediatric cancer, 5-year survival exceeds 85% in 1 to 14-year-olds and is significantly lower in adolescents at 75%.[3]

Barriers to Clinical Trial Participation in Underserved Groups

Individuals from racial and ethnic minority groups in the United States have a similar level of willingness to enroll in cancer clinical trials compared with non-Hispanic White patients.[38] Nevertheless, multilevel barriers prevent clinical trial enrollment at rates comparable to non-Hispanic White patients.[36] These include structural, clinical, attitudinal, and sociodemographic barriers at the institutional, physician, and patient levels. Structural barriers include clinical trial availability and complexity of trial design, time constraints for proper informed consent and enrollment paperwork, and lack of dedicated research staff to serve minority populations.[43] Clinical barriers related to patient ineligibility due to narrow eligibility criteria in some trials may limit generalizability of results. Sources of funding may impede equitable participation of minority individuals in clinical trials, as an increasing number of pediatric cancer clinical trials are sponsored by the pharmaceutical industry. Lack of diverse representation in clinical trials can be exacerbated when pharmaceutical companies seek a homogenous trial population to minimize confounding patient-related factors, while also attempting to open trials at high-enrolling sites, which tend not to be minority-serving institutions, particularly for adults, and where care appears to be more expensive.[44,45] At the physician level, physician preference has been described as a primary reason for nonenrollment of eligible patients.[36] Physicians play a pivotal role in clinical trial enrollment, because patients may only be aware of research opportunities and consider

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enrollment if recommended by their physician. Physicians may not offer a clinical trial if they think it may interfere with the physician-patient relationship. Moreover, racial/ethnic stereotypes may lead to the perception that minority patients are less likely to follow-up with the often-complex requirements of a clinical trial, resulting in the opportunity to participate not being offered. Lastly, patient-level factors include negative misconceptions about research or lack of awareness of clinical trials; fear of side effects, experimental procedures, or random assignment; health literacy, culture, and language barriers; transportation barriers; travel costs; insurance barriers; and unavailability of child care.[46] Moreover, mistrust of the health care and clinical trial systems has been cited by minority patients as a common reason for nonenrollment, particularly by Black individuals who have historically suffered discrimination by the medical system.[47]

Strategies to Increase Enrollment of Minority Populations in Pediatric Cancer Clinical Trials

It is critical that the demographics of patients enrolled in clinical trials of novel cancer therapeutics be comparable to that of the current U.S. pediatric population with cancer. Representative participation in clinical trials that support cancer discovery can ensure investigation of genomics associated with ancestry as well as consideration of health care delivery approaches necessary to maximize cancer care tailored to underserved patients. The U.S. racial/ethnic composition has changed rapidly over the last 50 years and is projected to continue to do so.[48] For instance, in 2010, 16% of the U.S population comprised Hispanic individuals, and by 2065, they are expected to comprise 31%; therefore, efforts to improve enrollment of minority patients are clearly needed, and we must prepare to provide state-of-the-art care to this growing population.[33] Barriers may differ among academic and nonacademic institutions; thus, approaches to optimizing clinical trial enrollment should be tailored to specific settings. Strategies to improve minority enrollment should address structural barriers related to study design and conduct, including informed consent. Decreasing the rigidity of inclusion/exclusion criteria facilitates enrollment of a study population that is a better reflection of patients who are most likely to receive those therapies in the real world. Partnerships between National Cancer Institute–designated comprehensive cancer centers and minority-serving institutions or satellite sites in underserved communities can be established to increase enrollment.[38],[49] Additionally, programs at ASCO[50] and the National Cancer Institute, such as the Center to Reduce Cancer Health Disparities,[51] facilitate the training of cancer scientists from diverse backgrounds to address the diversity gap in the pediatric oncology workforce, currently comprising 6.0% Hispanic and 1.5% Black providers.[52]

To overcome provider-level barriers, training focused on patient-provider communication, the use of culturally appropriate tools and medical interpreters, and employment of trained bilingual/bicultural research staff can facilitate minority enrollment. At the patient level, strategies, such as building trust, promoting education and awareness of clinical trials with anticipatory guidance and multimedia, and implementation of health literacy–focused interventions, that are also culturally and linguistically concordant may increase enrollment. Initiatives to address patients' socioeconomic barriers, such as reimbursement for food and/or transportation costs, coupled with allocation of funds to provide additional staff

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time for minority enrollment, may have a beneficial impact on enrollment and retention of minority individuals.[46]

Barriers and Enablers to Adequate Informed Consent in Minority Parents of Children With Cancer

Research is scarce on the factors that affect informed consent during enrollment of patients from minority groups in pediatric cancer clinical trials.[53,54] Studies indicate that barriers to adequate informed consent limit minority child and adolescent participation in clinical trials.[40,55,56] True informed consent is deemed valid and meaningful if competence, information disclosure, comprehension, and voluntariness are effectively satisfied.[55,57,58] The process involves the consenting provider verifying the participant's understanding of risks, benefits, and alternatives and ensuring patient's decision-making abilities.[59] Voluntariness is defined as the willingness to participate in research without feeling coerced.[60] Federal law requires that children and adolescents have parental informed consent to participate in research, but no mandates ensure voluntariness or comprehension of the information received.[53] Recruitment into pediatric cancer clinical trials often occurs under tremendous emotional stress because of the life-threatening nature of cancer and the need to start treatment promptly. This may hinder comprehension of the informed consent, parental decision-making abilities to weigh the benefits and risks in research, and voluntariness of participation in the clinical trial,[61] particularly in those with limited health literacy.[55,62]

Health literacy is defined as the degree to which individuals are able to process health information to make appropriate health decisions.[63] In the United States, at least one in four adults has limited health literacy skills.[64] Limited health literacy is associated with minority race/ethnicity and poor health outcomes in children.[64,65] Among children with cancer, limited health literacy has been associated with Hispanic ethnicity, Spanish language, low education level, and public insurance coverage.[55] In a recent report, lower perception of voluntariness was associated with limited health literacy among parents of children with newly diagnosed leukemia who had consented for their child's participation in a therapeutic clinical trial,[55] suggesting that parents with limited health literacy perceive external influences on their decision to enroll their child in a clinical trial. This highlights the potential role of recruitment interventions tailored to the participant's health literacy level to improve comprehension, decision-making abilities, and voluntariness of informed consent in underserved populations.[55] Interventions to increase minority recruitment in clinical trials have focused on communities rather than individuals,[66] with scant information on improving patient-provider communication during recruitment and informed consent procedures. Moreover, research is scarce on interventions to improve clinical trial participation in minority children and adolescents with cancer, particularly parental informed consent comprehension and decision-making self-efficacy. Future areas of research must include evaluating the feasibility and effectiveness of interventions designed to enhance shared decision-making and patient-provider communication during informed consent, including parent advocates and patient navigators and clinical trial education and anticipatory guidance with multimedia.[55]

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Racial, Ethnic, and Poverty-Associated Outcome Disparities Persist in the Clinical Trial Setting

Even when treated in multicenter clinical trials, children who are Black, Hispanic, or living in poverty experience higher rates of relapse and lower OS across disease groups.[10,67–70] The persistence of these disparities within the gold-standard setting of trial-delivered care underscores an urgent need to systematically incorporate social determinants of health into clinical trial design while concurrently developing evidence-based interventions to address them.

Acute Leukemia

A review of published trial data from the 1980s to the modern era demonstrates that Black and Hispanic children, and those who were exposed to poverty, experience excess relapse and death when compared with their non-Hispanic White, wealthier counterparts. Among 5,086 children with acute lymphoblastic leukemia enrolled in phase III Pediatric Oncology Group trials from 1981 to 1994, Black and Hispanic children experienced strikingly inferior OS compared with non-Hispanic White children (OS: 68.6% Black, 74.9% Hispanic, and 81.9% non-Hispanic White; $p < .0001$).[71] After adjusting for disease and treatment-era characteristics, Black race (HR, 1.42; 95% CI, 1.12–1.80) and Hispanic ethnicity (HR, 1.33; 95% CI, 1.19–1.49) remained independently associated with increased risk of mortality. A retrospective analysis of 8,762 children with acute lymphoblastic leukemia treated on Children's Cancer Group protocols demonstrated nearly identical survival disparities,[10] recapitulating the independent association of Black race (OS: relative risk, 1.4; 95% CI, 1.1–1.6; event-free survival: relative risk, 1.4; 95% CI, 1.2–1.7) and Hispanic ethnicity (OS: relative risk, 1.4; 95% CI, 1.2–1.6; event-free survival: relative risk, 1.3; 95% CI, 1.2–1.5) with inferior OS and event-free survival in multivariable analyses.

Similar racial and ethnic disparities exist in acute myeloid leukemia, a disease for which treatment is characterized by primarily inpatient chemotherapy and supportive care in contrast to the primarily outpatient cancer therapy used for acute lymphoblastic leukemia. Among 791 children with acute myeloid leukemia treated in CCG-2891 between 1989 and 1995, Black and Hispanic children had inferior OS compared with non-Hispanic White children (OS: Black, 34 ± 10%; $p = .007$; Hispanic, 37 ± 9%; $p = .016$; and non-Hispanic White, 48 ± 4%).[68] These disparities persisted in the subsequent decade in the cohort of 850 children treated in CCG-2961 between 1996 and 2002. Notably, Black and Hispanic children were more likely to experience death during induction ($p = .02$) and die of an infectious complication ($p = .035$) compared with non-Hispanic White children.[68,72]

The impact of socioeconomic status on acute lymphoblastic leukemia outcomes in the clinical trial setting has been less robustly investigated, in part because of historical deficiencies in the systematic collection of measures of socioeconomic status and other social determinants of health in cooperative group trials. A retrospective analysis of 575 children with newly diagnosed acute lymphoblastic leukemia treated in consecutive Dana-Farber Consortium Protocols between 2000 and 2010 demonstrated that children living in high-poverty areas were significantly more likely to experience early relapse (fewer than 36 months in complete remission) compared with those living in low-poverty areas.[67]

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Specifically, among the cohort of children who relapsed, 92% of those from high-poverty areas experienced early relapse, compared with 48% of those from low-poverty areas (p = .008). Black and Hispanic children were significantly more likely to live in high-poverty areas (p < .0001).

These retrospective trial data identify striking disparities but are unable to unravel the mechanisms underlying these survival inequities. Specifically, the relative contributions of social determinants of health associated with the social construct of racial/ethnic minority status (e.g., structural racism impacting socioeconomic status, education, access to health care, and basic resource needs) and genetic ancestry–associated pharmacogenomic differences[73,74] that may drive treatment efficacy or toxicity remain unclear. It is notable that similar analyses at St. Jude Children's Research Hospital for acute lymphoblastic leukemia between 1991 and 1998[75] and for acute myeloid leukemia between 1980 and 2002[76] demonstrated no differences in event-free survival or OS for Black or Hispanic children, perhaps due, in part, to systematic provision of social support in their model of care delivery, regardless of insurance coverage.

Lymphoma

Racial and ethnic disparities have been identified among children treated for Hodgkin lymphoma in the context of both Children's Oncology Group and St. Jude Children's Research Hospital[77] clinical trials, though investigation of trial-based disparities for other lymphomas are limited. Among a cohort of 1,605 patients with Hodgkin lymphoma treated in Children's Oncology Group trials between 2002 and 2012,[69] non-White patients (pooled Black and Hispanic) had a 1.88 (95% CI, 1.06–3.33) times higher risk of mortality in multivariable analyses adjusting for disease-associated characteristics. Among a subcohort of children with relapsed Hodgkin lymphoma, Black and Hispanic children experienced 3.45 (95% CI, 1.46–8.16) and 2.72 times (95% CI, 1.19–6.23) higher risk of postrelapse mortality, respectively, in multivariable analysis adjusting for neighborhood-level poverty. In a St. Jude Children's Research Hospital cohort of 327 patients with Hodgkin lymphoma treated in successive trials between 1990 and 2001,[77] Black children had inferior event-free survival compared with non-Hispanic White children (71 ± 6.1% vs. 84 ± 2.4%; p = .01) and were 3.7 times (95% CI, 1.7–8.0) as likely to relapse 12 months postdiagnosis.

Solid Tumor

Relatively few studies have investigated racial, ethnic, or socioeconomic disparities in clinical trials for pediatric solid tumors. A retrospective analysis of 2,343 children treated in Intergroup Rhabdomyosarcoma Study Group clinical trials between 1984 and 1997 identified no differences in failure-free survival between Black children and non-Hispanic White children.[78] Conversely, a more recent analysis of poverty exposure and survival in high-risk neuroblastoma demonstrated profound survival disparities among children with public insurance and those living in low-income areas. Among 371 children with high-risk neuroblastoma treated in Children's Oncology Group targeted immunotherapy trials ANBL0032 and ANBL0931 from 2005 to 2014, household poverty–exposed children experienced significantly inferior event-free survival (HR, 1.90; 95% CI, 1.28–2.82; p = .001) and OS (HR, 2.79; 95% CI, 1.60–4.79; p < .001) compared with poverty-unexposed

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children after adjustment for disease and treatment factors.[70] Although neighborhood poverty was not independently associated with survival, dual poverty exposure (household and neighborhood poverty) predicted both inferior event-free survival (HR, 2.21; 95% CI, 1.48–3.30; p < .001) and OS (HR, 3.70; 95% CI, 2.08–6.59; p < .001) in multivariable analyses. Neither race nor ethnicity was independently associated with inferior event-free survival or OS in this cohort; however, Black and Hispanic children were much more likely to be poverty-exposed and thus disproportionately suffered from poverty-associated survival disparities.[70]

Next Steps: Leveraging the Clinical Trial Infrastructure to Investigate and Address Disparities

Although limited to retrospective analyses, these data highlight the stark persistence of racial, ethnic, and socioeconomic disparities in clinical outcomes even in the context of clinical trial–delivered care. More studies are needed to examine differences in outcomes proximal to mortality. For example, among a cohort of 1,240 patients enrolled in Children's Oncology Group trials between 2010 and 2018, Black patients were significantly less likely to receive proton radiation therapy compared with non-Hispanic White patients (odds ratio, 0.35; 95% CI, 0.17–0.72; p = .004) even after adjusting for sociodemographic and disease-associated characteristics.[79] Access to radiotherapy, surgery, and stem cell transplant may impact survival outcomes for underserved children despite enrollment in uniform clinical trials.

That Black, Hispanic, and poor children with cancer are more likely to relapse and die when receiving cancer therapy in multicenter clinical trials highlights the stark reality that access to and equitable enrollment in clinical trials are necessary but not sufficient to eliminate survival disparities in pediatric oncology. More specifically, trial-embedded investigations of structural, sociobehavioral, and biologic mechanisms underlying racial, ethnic, and socioeconomic disparities are essential to inform evidence-based interventions aimed to achieve equity. Reporting of racial/ethnic outcomes in National Institutes of Health-funded trials is very low at approximately 13%, suggesting that National Institutes of Health policies mandating reporting of outcomes by race/ethnicity have not been effective.[32] Recent reports have demonstrated that clinical trial–embedded collection of parent-reported social determinants of health is feasible,[80] a first step in establishing the evidence base necessary to support trial-embedded health equity interventions. Preliminary data from these efforts demonstrate a high frequency of modifiable poverty exposures, including one in three children living with household material hardship (food, heat, housing, or transportation insecurities),[81] which disproportionately impact Black and Hispanic children.[80] Evaluation of a scalable intervention targeting household material hardship as a risk factor for outcome disparities is ongoing.[82]

Global Pediatric Cancer Disparities

Pediatric cancer inequities at the global level are even more striking than those observed in the United States and are essential to acknowledge in any discussion of pediatric oncology disparities. With more than 400,000 new cases of childhood cancer diagnosed annually worldwide,[83] the survival gap for children with cancer in low- and middle-

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income countries compared with high-income countries is astounding.[84,85] Unfortunately, in low- and middle-income countries, where 80% of the world's children reside, 5-year OS for children with cancer is 10% to 60%, compared with over 80% in high-income countries.[86] This survival gap reflects the profound disparities that exist in the socioeconomic and health care infrastructures between low- and middle-income countries and high-income countries that hinder access to comprehensive cancer care. Effective management of pediatric cancer involves obtaining accurate epidemiologic data, providing workforce specialty training, developing treatment and supportive care guidelines, ensuring consistent access to medications and equipment, improving patient/family psychosocial and financial support, and facilitating adherence to treatment. Contributing factors to disparate outcomes in low- and middle-income countries include inadequate training for health care providers, high rates of advanced disease at presentation, deficiencies in the referral and diagnostic pathways, malnutrition, high rates of treatment complications and abandonment, and limited access to curative therapies, such as chemotherapy and sophisticated surgical and radiotherapy services.[87-90] Global pediatric cancer programs are desperately needed to reduce survival gaps in low- and middle-income countries. Key components of such programs include financial coverage, accreditation of pediatric cancer centers, mandatory case registration and reporting, and the creation of national standards of care and pediatric cancer–governing bodies.[91] Strategies must focus on overcoming local challenges, leveraging regional opportunities, and engaging in capacity-building through the development of infrastructure, technology, and training for health care professionals to advance their ability to effectively care for underserved children with cancer in low- and middle-income countries.[92,93] Long-lasting improvements in disparate outcomes in low- and middle-income countries will require cohesive global health system planning with multiple stakeholders and establishing partnerships between institutions in high-income countries and low- and middle-income countries aimed at developing large-scale collaborative projects and research that have the potential to change national and international health policy.[86]

CONCLUSION

Pediatric oncology is a success story of modern medicine, with steady improvements in relapse and survival over the past half century ensuring that the great majority of children diagnosed with cancer in this era will be long-term survivors. That our most underserved children—those identified as from racial and ethnic minority groups and those of lower socioeconomic status—remain more likely to relapse and die of cancer is unacceptable. Overcoming pediatric cancer inequities is a moral and ethical imperative.

Pediatric oncology, as a field, is uniquely positioned to achieve the scientific breakthroughs necessary to eliminate outcome disparities by leveraging its robust cooperative group trial infrastructure to systematically identify mechanisms underlying disparities and evaluate health equity interventions to target them. Focusing future efforts on underserved and socially vulnerable children who experience increased morbidity and mortality represents the 21st century opportunity for continued improvements in pediatric cancer survival (Sidebar 1). To understand, address, and reduce disparities, epidemiologic and health outcomes research, including the development of multilevel strategies, is urgently needed within academic, health care, government, and community organizations. As pediatric

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cancer incidence continues to increase and minority populations continue to grow in the United States, it is time for a paradigm shift to integrate health equity investigation across all domains of pediatric cancer research—from biobanking to clinical trial development—to ensure every child has an equal opportunity for a cure.

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PRACTICAL APPLICATIONS

- Cancer health disparities, defined as systematic and avoidable differences in cancer incidence, burden, mortality, and survivorship that adversely affect underserved groups, are prevalent in pediatric cancer, a highly curable disease.
- Disparate outcomes prevail despite advancements in treatment and a high proportion of patients being treated in therapeutic clinical trials. The field of pediatric cancer disparities, although nascent, is growing, and efforts are ongoing to understand and effectively address disparate clinical outcomes and ensure health equity.
- Disparities in pediatric cancer are complex and multifactorial, and involve social determinants of health, as well as inequities in access to high-quality diagnostic procedures and treatments; supportive, psychosocial, and survivorship care; and clinical trials.
- To effectively achieve equitable survival in the United States and globally, domestic and international collaborative research efforts are urgently needed to gain a better understanding of factors underlying disparate outcomes and inform multilevel interventions across patients, caregivers, providers, health systems, and academic and payer organizations.

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SIDEBAR 1.

FUTURE AREAS OF FOCUS FOR PEDIATRIC CANCER DISPARITIES RESEARCH

- Health outcomes, cost-effectiveness, quality improvement, and implementation science research to scale up, evaluate, and disseminate evidence-based interventions (e.g., patient navigation and resource equity) to achieve equitable care for underserved children with cancer
- Approaches to raise awareness about pediatric cancer disparities in health care institutions and systems and broader communities, domestically and globally
- Empowerment of patients from minority groups and their caregivers to be active participants in their care and related research
- Dissemination of data to government and private sector health care insurers and policy makers regarding the need for high-quality care for underserved children and for development of health policies to achieve equitable outcomes for all

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TABLE 1.

Strengths and Limitations of Data Sources Used to Investigate Disparities

	Cancer Registry Data	Billing/Administrative Data	Clinical Trial Data	Institutional Data
Strengths	Full population-based sample, curated cancer data, and mortality data	Detailed information about medications, procedures, and hospitalizations	Targeted and consistent data collection on disease biology, treatment, and outcomes	Detailed electronic health record data and ease of primary data collections (surveys, interviews, patient-reported outcomes)
Limitations	Detailed clinical and treatment data are lacking	Difficult to identify patients with cancer and lacking clinical details	Selected population who only includes those enrolled in a research study	Limited sample size and generalizability

NOTE. None of these data resources consistently collect individual measures of socioeconomic status.

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