Title

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Journal

Pediatric Hematology and Oncology, 35(2)

ISSN

0888-0018

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Publication Date

2018-02-17

DOI

10.1080/08880018.2018.1464088

Peer reviewed

An Overview of Disparities in Childhood Cancer:

Report on the Inaugural Symposium on Childhood Cancer Health Disparities, Houston, Texas, 2016

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Abstract. The Inaugural Symposium on Childhood Cancer Health Disparities was held in Houston, Texas, on November 2, 2016. The symposium was attended by 109 scientists and clinicians from diverse disciplinary backgrounds with interests in pediatric cancer disparities and focused on reviewing our current knowledge of disparities in cancer risk and outcomes for select childhood cancers. Following a full day of topical sessions, everyone participated in a brainstorming session to develop a working strategy for the continued expansion of research in this area. This meeting was designed to serve as a springboard for examination of childhood cancer disparities from a more unified and systematic approach and to enhance awareness of this area of need.

Introduction. The Inaugural Symposium on Childhood Cancer Health Disparities was held at Texas Children's Hospital in Houston, Texas on November 2, 2016, with the objective of bringing together researchers and clinicians to develop a unified agenda on addressing disparities in childhood cancer. While the mortality due to childhood cancer has been decreasing since the 1970s, overall incidence has increased over the same period.[1] A recent review of cancer research projects funded by the National Cancer Institute suggests that less than 5% of the overall budget is spent on pediatric cancer. Further, a majority of those funds are for projects investigating the basic biology of pediatric cancers and developing novel therapies. While there are documented disparities in childhood cancer, both in terms of susceptibility and outcome, very little is known about why these disparities exist. Additionally, because childhood cancers are relatively rare, it is often difficult to evaluate these issues. The symposium sought to review the current state of knowledge and stimulate collaborative research in the area. The program included two lectures on the epidemiology of childhood cancers in the United States and across the globe and four sessions that focused on known disparities in childhood cancer; this was followed by a brainstorming session to outline a research agenda to move the field forward. A summary of the scientific content of the symposium and our suggestions on a future research agenda are provided in this report.

Global Burden of Childhood Cancer (J. Schüz)

Childhood cancer is rare. In fact, it accounts for less than 1% of all cancers in developed countries, although it makes up 4-5% of all cancers in Sub-Saharan Africa

due to the young average age of their population. It is estimated that, on a global scale, there are annually 215,000 new cases of childhood cancer (estimated by the World Health Organization/International Agency for Research on Cancer for the World Childhood Cancer Day 2016), based on observations from cancer registries and extrapolations to the world population. However, high-quality cancer registries exist mainly in high-income countries, with good coverage in North America and Australia, while only about half of the population of Europe is covered by cancer registries and less than 10% in Africa, Latin America, and Asia. Hence the estimate of 215,000 has to be interpreted with care. Two observations stem from these data. First, there is large geographical variation, with highest incidence rates of 160-170 per million in children in some developed countries and <50 per million in some developing countries, especially in rates of acute lymphoblastic leukemia (ALL), which is the most common type of childhood cancer.[2] Second, at the same time, there is surprisingly little variation in ALL rates between non-neighboring developed countries such as Australia, Germany, and the USA. Hence, the reason for the incidence differences could be variation in underlying risk factors, genetic predisposition or a mixture of both, which may be common in all developing countries irrespective of which continent they belong and less common in many developing countries. Alternatively, rates may be affected by a lack of diagnosis, treatment, and hence, registration, of some cases in low-income countries. As a hypothetical scenario using the 2015 childhood population of the World Bank, under the assumption of the incidence rate being equally high around the world at the highest measured incidence rate, the number of new cases would increase to 330,000

per year, some 50% higher. Only improved health cancer and better cancer registration will give more reliable figures in the future.

The annual number of childhood cancer deaths on a global scale was estimated to be 80,000, but could be as high as 180,000 under the hypothetical scenario (as the vast majority of the undetected or untreated cases would be expected to die of their disease). Mortality shows massive disparities around the globe. While the incidence-to-mortality ratio is >7 in North America it is less than 2 in Africa and Asia. The impressive improvements in therapy, in particular for ALL survival reaching now >90% in many developed countries, have not reached all parts of the world, and survival remains poor in many sub-Saharan African and low-income Asian countries. Some disparities, however, are also seen within high-income countries, and even for social welfare states such as Denmark it was reported that survival rates of childhood cancer somewhat differ by socioeconomic and family indicators.

Childhood Cancer Disparities in the United States (L. Spector)

The ethnic composition of the U.S. has changed rapidly over the last fifty years and is projected to continue to do so.[3] For instance, in 2010 Latinos comprised 16% of the U.S. population and by 2065 they are expected to comprise 31%. The extent to which ethnic differences in incidence and survival of childhood cancer are due to socioeconomic circumstances versus biological predisposition is not known, although for some cancers the biological explanation appears favored. For instance, the rate of ALL among black children remains half that of white children even after adjusting for

well-known perinatal risk factors.[4] Moreover, several variants which increase susceptibility to ALL are less common in black children and may explain a proportion of the disparity in incidence.[5] On the other hand, a recent immigrant study in California found that the rates of several childhood cancers among children with Mexican ethnicity approached those of children with European ancestry if their mothers had been born in the U.S. (a rough measure of acculturation) but not if they had been born in Mexico,[6] suggesting that some aspects of the U.S. lifestyle may modify risk.

Session 1. Acute Leukemias among Ethnic/Racial Minorities (K. Rabin – moderator)

Genetic and Infectious Factors in Childhood Leukemia Risk (J. Wiemels)

Since 1975 there has been an overall 35% increase in incidence of childhood leukemia. Hispanic children have experienced an annual increase of 1.3% compared to only 0.5% annually for non-Hispanic white children.[7] Genome-wide association studies (GWAS) have identified several risk loci for childhood leukemia[8-14]; however, many of these studies have been conducted among non-Hispanic white populations. While Walsh et al. reported that for every 20% increase in Native American ancestry there was a corresponding 20% increase in the risk of B-ALL among Hispanic children [15], this increase was incompletely accounted for by existed genetic variants which increase ALL risk, some of which have a higher allele frequency among Hispanics. Additional GWAS to identify specific Hispanic risk loci are currently underway.

There is long-held evidence that early life infections play a role in leukemia risk. In a meta-analysis, Urayama et al reported an overall 23% reduction in risk of childhood leukemia when daycare attendance was reported in childhood.[16] Ma et al. also reported that this inverse association was different among Hispanic children when compared to non-Hispanic whites.[17] Recently, infection by cytomegalovirus was associated with increased risk of ALL; this appeared to be a stronger risk factor for Hispanics than non-Hispanic whites [18]. de Smith and colleagues have found that the presence of activating KIR receptors, which instruct natural killer cells recognize and eliminate cancer cells, were associated with reduced risk of leukemia in Hispanics but not Non-Hispanic whites.[19] Clearly, genetic factors appear to explain some of the disparities in leukemia incidence and may modify responses to infectious environment.

Racial Disparities in Pediatric Leukemia Outcomes (R. Aplenc)

Previous cooperative group trials have consistently demonstrated inferior survival among African-American children with acute myeloid leukemia (AML) compared to whites.[20,21] The basis for this disparity has yet to be elucidated; however, several factors are likely to play a role, including: differences in disease biology, response to chemotherapy, availability of supportive care, access to care, and enrollment on clinical trials. Aplenc and colleagues have utilized the Pediatric Health Information Systems (PHIS) database as a resource to improve the understanding of the etiology of racial disparities in outcomes among children with AML. PHIS data consist of diagnostic codes and daily inpatient billing information from 46 free-standing pediatric hospitals in the U.S. and has been used in over 500 peer-reviewed research publications.[22-28] This valuable resource is highly complementary to the data captured on large cooperative

group trials as PHIS includes daily resource utilization data not available in clinical trial datasets. Using PHIS data from 2004-2014, they investigated the specific question of disparities in induction mortality rates for pediatric AML. The study included 1,122 patients with pediatric AML; 84% were white and 16% were African-American. African-American children were significantly more likely to have public rather than private insurance (54.5% vs. 37.8%, $p<0.001$); to be in the lowest quartile of median household income (38.9% vs. 22.4%, $p<0.001$); and to have greater acuity of presentation (i.e., require admittance to the intensive care unit or present with multi-organ system failure in the first 72 hours of hospitalization; 16.9% vs. 11.1%, $p=0.032$). The PHIS study identified an unadjusted higher rate of induction mortality among African-American children (4.9% vs. 1.9%, $p=0.04$), and on adjusted mediation analyses demonstrated that higher acuity at presentation accounted for 61% of the excess induction mortality after accounting for insurance and SES status (HR=1.53, 95% CI: 1.08-2.17, $p=0.015$).

A follow-up study utilizing electronic medical records (eMR) to further investigate the factors responsible for this higher rate of induction mortality is underway through a collaboration between the Children's Hospital of Philadelphia and Texas Children's Hospital. The groups have designed an automated interface for eMR data extraction and deposition in a centralized database, supplemented by manual abstraction of key clinical data. These data will enable examination of severity of illness at presentation and the association with geographical residential data.

Biologic Contributors to Leukemia Outcome Disparities Among Hispanics (M. Gramatges)

Hispanic children diagnosed with acute leukemias have worse survival than non-

Hispanic whites (NHW). Reasons behind this outcome disparity are likely multifactorial, related to a combination of geographic and socioeconomic barriers, ethnic-related differences in disease biology and pharmacogenomics, as well as other host factors contributing to risk for therapy-related toxicities. This section discusses the impact of ethnicity upon acute leukemia outcomes, with a focus on pediatric AML. Among children diagnosed with AML, favorable cytogenetics, including inv(16) and t(8;21), are associated with an up to 30% increase in overall survival (OS) when compared with AML with normal karyotype.[29] In a report of two studies from the Children's Cancer Group, Hispanic children had an increased, though not statistically significant, incidence of AML with t(8;21) compared with non-Hispanic whites (NHW).[20] However, among both pediatric and adult AML populations where a similar cytogenetic distribution has been observed, outcomes for Hispanics are consistently similar or inferior to that of NHW.[20,30] In a retrospective review of 167 children ages 0-18 years diagnosed with AML at Texas Children's Hospital, we also observed a significant enrichment of AML with t(8;21) among Hispanics compared with NHW (p=0.04). Similarly, no difference was detected in event-free or OS, although Hispanics demonstrated a trend toward shorter time to relapse. However, Hispanic children in this study who were treated with up-front hematopoietic stem cell transplantation (HSCT) had significantly poorer OS than NHW (28.6% vs. 76.5%, p = 0.008), primarily due to relapse.[31] This finding suggests that a subpopulation of Hispanics is at higher than expected risk for poor outcomes, and may be contributing to the overall trends observed in outcome disparities. Some studies have also suggested a higher risk of death from infectious complications in Hispanic children with AML.[20] Over a 10-year period, Hispanic children diagnosed with acute

leukemias at our institution were more likely to develop an invasive mold infection than NHW (p=0.04, unpublished data). Research is underway to explore host factors that may be related to this observation, such as a higher incidence of hyperglycemia or metabolic syndrome among Hispanics, or disparities in duration and severity of immunosuppression in response to chemotherapy. Capacity for bone marrow recovery is related to cellular telomere length, the protective DNA-protein caps on chromosome ends that shorten with DNA replication. A recent study in children with AML showed short blood telomere length at end of leukemia induction predicts significant delays in hematopoietic recovery, defined as prolonged neutropenia, in later courses of chemotherapy.[32] Though a relationship between short telomere length, prolonged neutropenia, and infection incidence remains understudied, Hispanics appear to have shorter blood telomere length than NHW [33], and Hispanic children and young adults with AML are more likely to have telomere length in the less than 10th percentile than NHW (p=0.04, unpublished data). Together, these results are suggestive of ethnic disparities in AML disease biology, response to therapy, and risk for therapy-related toxicities. Validation of these findings in a large, ethnically diverse leukemia cohort, perhaps through multi-institutional collaboration, may influence clinical decision-making in future treatment trials and uncover therapeutic strategies to address these disparities.

Session 2. Genetics of Health Disparities (P. Lupo – moderator)

SNPs, Genes, and Race: Tracking the perfect storm in Ewing sarcoma (J. Schiffman)

Ewing Sarcoma is the second most common bone tumor in children and adolescents. Nevertheless, it remains quite rare and occurs in 3:1,000,000 people less than 20 years old. This sarcoma is found to be slightly higher in males. Interestingly, Ewing sarcoma is much more common in Caucasians and rarely is diagnosed in patients with Asian and especially African ancestry. Despite these striking differences in racial predilection, Ewing sarcoma is currently considered to be non-familial (i.e., no known genetic predisposition).[34] Another pronounced epidemiological finding is the association of Ewing sarcoma in several different studies with hernia risk in patients and their family members.[35] The rare patients with Ewing sarcoma who are non-Caucasian consistently have a worse clinical outcome, highlighting an important outcome disparity in this disease.[36] We do know that polymorphic GGAA repeat microsatellites have been associated with Ewing sarcoma somatic transformation, as well as recent GWAS [37-42]; in fact, one of the candidate SNPs in recent GWAS for Ewing sarcoma has been linked to GGAA microsatellite region.[40,43] Since the Disparity Conference, a recent publication has described pathogenic or likely pathogenic germline mutations in 13.1% of a cohort of patients with Ewing Sarcoma (N=175) [44]; these included pathogenic mutations in DNA damage repair genes associated with cancer predisposition syndromes. Nevertheless, Ewing sarcoma is still not considered to be representative of a recurring cancer found in any of the inherited genetic predisposition syndromes. The development of Ewing sarcoma most likely represents the rare combination of SNPs, gene variants, and racial background. To better explore the genetic epidemiology of Ewing Sarcoma, a large-scale study has been initiated to enroll familial trios of Ewing sarcoma along with family history, germline DNA, and clinical outcome called Project

GENESIS (Genetics of Ewing Sarcoma International Study [45]); the data analysis from this study is still ongoing, and it is hoped that the results will help to inform the disparities in disease risk and clinical outcome for Ewing sarcoma.

Childhood Leukemia and Genetic Predisposition in Brazil (M. Pombo-de-Oliveira)

As in several counties, acute leukemia is the most common pediatric malignancy in Brazil, accounting for ~25% of all cancer diagnoses in those <15 years of age.[46] While ~5% of these cases are associated with genetic syndromes, the remaining 95% are likely to arise from the interactions of multiple genes and environmental exposures (i.e., they are multifactorial conditions), and based on the evidence that leukemia-related somatic mutations arise *in utero*, several of these processes are likely to begin in the prenatal period. Because of that, the primary areas of childhood leukemia research conducted by the Brazilian Pediatric Hematology-Oncology Research Program have been: 1) early-age leukemia (EAL), i.e., those leukemias that affect neonates (≤31 days), infants (≤12 months), and toddlers (up to 24 months); 2) if there are key maternal exposures that are common in the Brazilian population that are associated with EAL; and 3) if xenobiotic gene polymorphisms modify the association between environmental exposures and EAL. Putative environmental exposures during pregnancy that have been evaluated include (but are not limited to) maternal smoking, exposure to pesticides, and with the excessive use of estrogen.[47-49] Additionally, in relation to estrogen, there is some evidence that genetic polymorphisms of estrogen metabolism are associated with EAL.[50] An important conclusion from this research is that these exposures (and related genetic variants) appear to have highly specific associations

with acute leukemia subtypes. Work is ongoing in this population to disentangle the origins of EAL.

Pharmacogenomics of Racial Disparities in ALL (J. Yang)

As noted, while survival for childhood ALL has steadily increased in recent decades, not all groups have benefited equally. There is emerging and consistent evidence that these disparities may have a genetic component. For instance, in one report, when considering four genetic ancestry groups, only Native American (NA) ancestry was significantly related to ALL relapse.[51] Interestingly, relapse risk conferred by NA ancestry was attenuated by additional chemotherapy: 8-year relapse rate was 17% in those with NA ancestry that received treatment intensification compared to 27% in those who had the same genetic background but did not receive treatment intensification [52], pointing to a potential therapeutic intervention to reduce racial difference in ALL outcomes. Racial differences in therapy-related toxicities have also been identified for ALL. In particular, thiopurine-induced myelosuppression is most severe in Asians. Notably, the *NUDT15* C416T variant was recently identified in a GWAS to be associated with the susceptibility to mercaptopurine (MP) intolerance [52] and explained a large proportion of ancestry-related differences in MP toxicity. Building from this evidence, work has progressed for dose modification strategies for patients with *NUDT15* risk variants.[53] Additionally, several investigators are working together to develop an international consortium to develop clinical guidelines to implement *NUDT15*-based treatment individualization. These findings point to the importance of pharmacogenetics-based precision medicine approaches for mitigating racial disparities in treatment

toxicity, which will improve outcomes and survival in these children.

Session 3. The Environment and Disparities in Childhood Cancer (M. Scheurer – moderator)

Pediatric Cancer and Environmental Pollution Disparities (J. Heck)

There is continued and growing concern over the role of traffic-related air pollution on the risk of childhood cancer. A recent meta-analysis conducted by Filippini et al reported an increased risk for childhood leukemia with exposure to greater traffic-related air pollution at the residential address, using different metrics for air pollution exposure. Increasing risk was reported for greater nitrogen dioxide (OR= 1.21, 95% CI 0.97-1.52), particularly for ALL (OR=1.21, 95% CI 1.04-1.41). Postnatal exposures were associated with greater risk than prenatal, although this may be an artifact of the study locations and methods, which varied. Benzene exposure was related to AML (OR=2.28, 95% CI 1.09-4.75) but not ALL.[54] Given this suggestion of increased leukemia risk from traffic-related air pollution, it may be informative to examine exposure to traffic across demographic and socioeconomic groups. In California Heck and colleagues conducted a study of childhood cancer risk and traffic exposure and estimated traffic risk using Land-Use Regression [55] and California Line-Source Dispersion (CALINE4) models [56]. Using the estimates generated in these studies, they reported on average traffic pollution exposures across the diverse population. Statewide, exposure to traffic is highest among African-American children, followed by Hispanic, Asian/Pacific Islander, and NHW children. Within racial/ethnic categories, there was not a clear increasing gradient with lower maternal education: among Black children, exposure to traffic was

high in every educational category, while among White children, the relation between traffic exposure and maternal education had a U-shaped relationship. The children of foreign-born mothers had higher exposure than the children of US-born mothers. Yet, when they looked within Los Angeles County alone, there was a clearer and more linear gradient between maternal education and traffic exposure, while the differences across ethnic groups dropped, with all minority groups having similar exposure patterns, although all minority groups had higher exposure than Whites. Patterns between disadvantage and pollution exposure, however, vary across nations [57], perhaps based upon historical housing patterns, which are rooted in economic factors as well as discrimination.

Differential Exposure to Potential Carcinogens in Latino Children (M. Orjuela-Grimm)

In a recent ecologic study, Kamihara et al reported that the incidence of neuroblastoma, retinoblastoma, and nephroblastoma was higher among children in more developed countries [58], possibly indicating that exposure to environmental pollutants could be contributing to the higher rates of cancer in these countries. Through the Columbia Center for Children's Environmental Health, Orjuela et al have been examining differential exposures to polycyclic aromatic hydrocarbons (PAHs) and potential mechanisms through which PAHs may be associated with carcinogenesis among inner city Dominican and African-American women in New York City. Prenatal exposure to PAHs significantly predicted presence of chromosomal aberrations such as translocations at birth (in cord blood) in large chromosomes (especially on chromosome 6) including those frequently involved in translocations commonly found in ALL after

adjusting for gender of the child, ethnicity, and exposure to household cigarette smoke.[59] Further, significantly elevated levels of PAH metabolites were found in urine from 5-year-old children who had stable chromosomal aberrations or translocations in concurrent blood samples compared with children without these translocations. In fact, children in the upper tertile of 2-naphthol levels (a metabolite of naphthalene, a PAH) had more than a four-fold increase in translocations compared to those in the lowest tertile. Together, this work suggests that elevated exposures to common air pollutants during pregnancy and early childhood, two periods relevant to pediatric leukemogenesis, are associated with formation of chromosomal translocations, an intermediate step in leukemogenesis, and may disproportionately affect some inner city children.

Environmental Exposures and Risk of Leukemia in Latino Children (C. Metayer)

A main objective of the California Childhood Leukemia Study (CCLS), which comprises about 40% of Latino children, is to examine ethnic differences in leukemia risk due to environmental exposures in the home and from the parents' jobs. Using detailed task-based questionnaires, Metayer et al. reported that paternal occupational exposure to chlorinated hydrocarbons and PAHs – both known carcinogens – increased the odds of having a child with leukemia, but only among Latino fathers.[60] This racial/ethnic difference in risk could reflect differences with respect to the types or lengths of exposures experienced, differences in genetic susceptibility to these toxicants, uncontrolled bias or confounding, or could be a surrogate marker for nearby environmental pollution (air, soil, or water). Latinos represent the largest agricultural workforce in California which uses the highest amount of pesticides in the US. In a

recent study, fathers exposed to agricultural pesticides had an elevated risk of having a child diagnosed with leukemia.[61] Leukemia risk was higher when fathers reported working on nut farms. Interestingly, harvesting nuts generates a lot of dust, which potentially exposes workers to pesticides via dermal absorption and inhalation. Another area of environmental concern on the risk of childhood cancer is parental smoking, especially maternal smoking during pregnancy or early in the post-natal period. A recent pooled analysis conducted through the Childhood Leukemia International Consortium reported an overall null effect of maternal smoking during pregnancy on risk of AML in offspring; however, when stratified by race/ethnicity, children of Latina mothers who smoked during pregnancy experienced a significant two-fold increase in risk of AML.[62] These results point to the need of developing prevention programs to reduce exposure to chemicals, especially among vulnerable populations.

Session 4. Social Determinants of Health in Pediatric Cancer (H. Russell – moderator)

Disparities in Access to Care Amongst Pediatric Cancer Patients (M. Austin)

Access to care is defined as the degree to which individuals and groups are able to obtain needed resources from the medical care system. Inequity in access is defined as systematic differences in use of health services and outcomes among groups that are the result of barriers to access. Barriers can be structural (e.g., availability of care, organization of care, transportation needs), financial (e.g., insurance coverage, out-of-pocket and indirect costs), or personal (e.g., culture, language, attitudes, education).

Collectively, these barriers influence a patient's use of services, which, along with mediators of use (e.g., appropriateness/quality/efficacy and adherence to treatment), affect patient outcomes. A recent study at Primary Children's Hospital in Salt Lake City reported that rural residents were particularly impacted by financial barriers to care.[63] A study using data from the Surveillance, Epidemiology, and End Results (SEER) program found that having public insurance or a lack of insurance are independently associated with higher stage of cancer at diagnosis for all adolescent and young adult (AYA) cancer types included in the study (i.e., breast, cervical, lymphoma, male genitourinary, skin, colon).[64] Smith et al found that being in the lowest socioeconomic quintile, lacking health insurance and being publically insured were associated with advanced stage Hodgkin lymphoma.[65] Hispanic children and those from low socioeconomic status (SES) were more likely to present with extraocular retinoblastoma, and Hispanic and black children were more likely to undergo enucleation than white children.[66] Further, enucleation rates were higher in disadvantaged counties again demonstrating potential inequities in access to appropriate care. Austin et al reported that Hispanic ethnicity was independently associated with advanced stage disease at presentation for CNS tumors, whereas Black race was associated with advanced stage disease in non-CNS solid tumors.[67-69] In melanoma, a small but unique subset of pediatric cancer patients, Hispanics were 4 times more likely to present with advanced stage melanoma.

Communication Challenges Faced by Parents of Children with Cancer: Understanding disparities (P. Aristizabal)

Unequal access to services and poorer health outcomes can be related to a variety of contextual factors, especially language and cultural barriers to communication with healthcare providers. Common barriers to communication include: poor coordination of care between providers, inability to communicate with patients with limited English proficiency, limited efficacy of interpreters, and lack of understanding of sociocultural differences and divergent beliefs.[70] Families with limited English proficiency often report less trust in provider who does not speak same language.[71] Communication with these families typically relies heavily on the use of interpreters and translated documents; however, even when a translator service is used, translation errors occur an average of 32 times per pediatric hospital visit.[72] Therefore, patients with non-English-speaking caregivers are more likely to experience significantly longer hospitalization stays and more frequent adverse side effects to medications.[73] These experiences often result in a decreased understanding of personal medical situations, decreased participation in research protocols [74], and a higher likelihood of prematurely ending treatment. Abandonment of curative therapy, regardless of the reason, can be especially detrimental to the survival of children with cancer.

Poverty and Childhood Cancer Outcomes (K. Bona)

Poverty is correlated with negative health outcomes in pediatric primary care and subspecialties [75-78]; however, the mechanism by which poverty impacts pediatric cancer outcomes is poorly understood [79-88]. Further, pediatric oncology providers do not routinely consider poverty as a risk factor for poor clinical outcomes; nor do they modify care delivery based on poverty. Non-adherence to oral chemotherapy is associated with approximately 60% of relapses among Hispanic and NHW children with ALL.[89] Children

living in areas of high poverty are more likely to relapse early (92% vs. 48%, p=0.008) and have a lower overall survival 85% vs. 92% (p=0.02).[90] It has been reported that family poverty is associated with decreased adherence to oral chemotherapy.[91]

Conclusions. This inaugural symposium was attended by 109 scientists and clinicians from diverse disciplinary backgrounds with interests in pediatric cancer disparities. Following the full day of topical sessions summarized above, everyone participated in a brainstorming and planning session designed to outline a future research agenda. The first realization was that the term “disparities” had many different meanings depending on who was speaking. In addition to the traditional thought of racial and ethnic disparities, we discussed the roles for gender, language preference, insurance status, socioeconomic status, and geographic location (e.g., rural setting, neighborhood deprivation) on both risk of cancer development and risk of adverse outcomes in pediatric cancer patients. We further discussed that many of these factors are not only relevant to the pediatric cancer patient, but to their parents/guardians and other family members as well.

To advance a research agenda in pediatric cancer disparities, there was strong support from all attendees for the need to better evaluate the exposures, social determinants, and genetic factors in our studies. First, it was felt that studies examining racial and ethnic disparities should include both measures of self-report as well as genetic ancestry, when possible. Several studies have pointed to the effects of genetic ancestry on both risk of certain cancers as well as on differences in outcomes. Furthermore, there is evidence that differences in both disease biology and host susceptibility

contribute to some of the racial/ethnic differences in risk of disease and poor outcomes. Second, there is a need for new approaches to gene-environment interaction studies, which are likely to be higher yield than studies of main effects alone. However, the greatest impediments to better interaction studies remain with difficulties in accurately measuring environmental exposures at the critical windows of development that are relevant for childhood cancers; generally small sample sizes; and an overall lack of obvious strong environmental risk factors. While studies using questionnaires have identified several chemicals associated with childhood leukemia and other cancers, future work is needed to identify relevant biomarkers of environmental exposures. Third, there was overwhelming support for advocating for the systematic and standardized collection of socioeconomic variables integrated into cooperative group trials. Therefore, we should work together to develop a consensus of the domains to be covered and the specific measures to be used for those domains. Once this consensus is reached, advocacy can begin to include these standard measures in all new clinical trials. Fourth, more work is needed to characterize the system-level variables that contribute to childhood cancer disparities**.** A more complete examination of SES and poverty at the individual and neighborhood level needs to be examined in relation to cancer outcomes. Additionally, the manner by which physicians communicate with patients and their families has an effect on likelihood to follow best guidelines for treatment and follow-up, which will affect overall outcome in those patients.

In addition to better characterizing the environmental and contextual exposures that might contribute to childhood cancer disparities (and therefore better targeting interventions to reduce disparities), it was also discussed that better phenotyping of our

outcomes is desperately needed. In this era of –omics research, we have the opportunity to begin to understand disparities in the context of a specific cytogenetic profile or somatic mutational landscape of a cancer that might be more prevalent among a specific subset of the patient population.

Finally, there was strong support for advocacy by the group for funding mechanisms to explore issues of disparities in cancer risk and outcome specifically among children and survivors of childhood cancer. The ultimate goal is to develop interventions for the clinic to affect outcomes in these patients. For example, research in the area of disparities could lead to opportunities for modified family education, integration of systematic screening for material hardship, and “risk-adapted” allocation of resources in the clinical setting.

This inaugural symposium focused on reviewing our current knowledge of disparities in childhood cancer risk and outcomes and developing a working strategy for the continued expansion of research in this area. We hope that this meeting will be a springboard for greater awareness of the need to examine childhood cancer disparities from a more unified and systematic approach.

Acknowledgements. We are thankful for the generous support for the symposium provided by Northwestern Mutual Foundation and Alex’s Lemonade Stand Foundation. We are also grateful to Texas Children’s Hospital for hosting the event. We would like to specifically thank the following people for their assistance with the organization of the symposium: Cindy Powers, Tarsha Boykin, Shanté Rodney, Shelly Groves Brandon,

and Jodi Nolte. Without their dedication to this event, it would not have been the success it was. The views expressed in written conference materials or publications and by speakers and moderators are their own and do not necessarily reflect the official policies of the sponsoring institutions.

Conflict of Interest Statement. All authors declare that there are no conflicts of interest.

Funding. Funding for the Symposium was provided by Northwestern Mutual Foundation and Alex's Lemonade Stand Foundation. J.D.S. holds an Edward B. Clark, MD, Chair in Pediatric Research from the Primary Children’s Hospital (PCH) Foundation. J.J.Y. received funding from the National Cancer Institute (U01 CA176063) for the work presented at the symposium. P.J.L. and K.R.R. received a St. Baldrick's Foundation Consortium Grant to further examine cancer disparities among Hispanic children with acute leukemias.

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