Request for INRG Data Analysis

<table>
<thead>
<tr>
<th>Proposal Title</th>
<th>Racial and Ethnic Disparities in Risk and Survival in Children With Neuroblastoma: An Updated Analysis Using the International Neuroblastoma Risk Group Database</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal Investigator and Co-Investigators</td>
<td>Caileigh Pudela, Ami V. Desai, Mark Applebaum, Tara O. Henderson, Susan L. Cohn</td>
</tr>
<tr>
<td>Institution</td>
<td>The University of Chicago</td>
</tr>
<tr>
<td>E-mail Address</td>
<td><a href="mailto:Caileigh.pudela@uchospitals.edu">Caileigh.pudela@uchospitals.edu</a>, <a href="mailto:adesai12@peds.bsd.uchicago.edu">adesai12@peds.bsd.uchicago.edu</a></td>
</tr>
</tbody>
</table>

**Specific Aims:**

Neuroblastoma is a clinically heterogeneous disease. Clinical features and biologic markers are prognostic of outcome and have been used to define risk groups and guide treatment strategies. Our previous studies have shown that children with neuroblastoma who are black and Native American have a higher prevalence of high-risk neuroblastoma resulting in worse event free survival (EFS) when compared to white children with neuroblastoma. In addition, a higher prevalence of late-occurring events among blacks with high-risk disease was observed [1]. A follow-up study demonstrated genetic variations contribute to differences in neuroblastoma phenotype and the ethnic disparities in presentation and survival in those with African genomic ancestry [2]. It has been nearly a decade since we evaluated the racial and ethnic differences in clinical and biologic risk factors and outcomes of patients with neuroblastoma enrolled on COG ANBL00B1 between 2001 and 2009 (analytic cohort, n=3,539) [1]. In the interim, there has been limited additional literature on racial and ethnic disparities and survival in children with neuroblastoma. The INRG Data Commons now contains data from ~21,000 patients, with 14,907 patients enrolled on a COG biology study and/or therapeutic trial. Thus, we now propose to investigate the relationships between race/ethnicity, clinical and biological factors, and outcomes in this new cohort of patients with neuroblastoma diagnosed between 2010-2016 in the INRG Data Commons to determine if the association between inferior outcome and African American race is maintained.

The specific aims of this study are:

1. To validate the association between African American race and increased prevalence of high-risk disease identified in a cohort of 3,539 neuroblastoma patients diagnosed between 2001-2009 in an independent cohort of patients diagnosed between 2010-2016.
2. To analyze racial and ethnic disparities in outcome over time and by risk group.
3. To determine if the higher prevalence of late-occurring events among blacks with high-risk disease compared with whites identified in patients diagnosed between 2001-2009 has been mitigated in a cohort treated between 2010-2016, when post-consolidation immunotherapy became part of standard of care.

**Hypothesis:**

We hypothesize that race and ethnicity continue to impact disease presentation and survival in an expanded cohort of patients with neuroblastoma. We also hypothesize that there will no longer be a higher prevalence of late-occurring events among black patients with high-risk disease, in part due to the introduction of anti-GD2 antibody into treatment.

**Patient Cohort (Eligibility Criteria):**

The analytic cohort will consist of the subset of patients in the INRG Data Commons enrolled on COG ANBL00B1 diagnosed between 2001-2016. Patients without race/ethnicity information available will
be excluded; therefore, our cohort is restricted to patients enrolled on a COG study with available race/ethnicity data. Risk stratification will be determined as previously described [3] or determined by therapeutic trial enrollment. Outcome data will be necessary for Aims 2 and 3. Clinical, biologic, treatment, and outcome data will be requested as detailed in the Data Requested section below.

**Background:**
Associations between race/ethnicity and clinical outcomes have been described for many cancers [4-6]. After analyzing twenty years of Surveillance, Epidemiology, and End Results Program (SEER) data for children with acute lymphoblastic leukemia (ALL), Goggins and Lo found that black, Hispanic, Native American, and Asian American children with ALL have significantly poorer survival than non-Hispanic white children with ALL [4]. Kahn and colleagues conducted a population-based study of children and adolescents with Hodgkin lymphoma (HL) and reported that Hispanic and black children with HL have a significantly higher hazard ratio of post-relapse mortality [7]. In children with retinoblastoma, Truong et al. found that Hispanic children have a higher percentage of extraocular disease at presentation and higher rates of enucleation. Additionally, survival of black children with retinoblastoma at five years was lower when compared with survival of non-Hispanic white children [8].

There is still relatively little known about ethnic disparities in presentation and outcome of children with neuroblastoma. Based on a 2011 analysis of 3539 patients with neuroblastoma, it was demonstrated that black and Native American children with neuroblastoma are more likely to present with high risk disease. Black children were found to present at an older age and with more unfavorable histology when compared with white children. Additionally, black and Native American children had significantly worse 5-year event-free survival, and there was a higher-prevalence of late-occurring events among black children with neuroblastoma [1].

The underlying causes of racial and ethnic disparities in presentation and outcomes of children with cancer are not entirely understood. Both biologic and socioeconomic pathways have been described in the literature. Among socioeconomic causes of disparity, decreased access to care leading to diagnosis delays and decreased enrollment in cooperative group trials have been described [9, 10]. Decreased adherence to therapy and surveillance for long-term toxicities have been suggested as reasons for racial and ethnic disparities in survival [9, 11]. Underlying differences in disease biology, pharmacogenetics, and genomics could also play an important role in differences in survival [9, 12, 13].

Because low-risk neuroblastomas rarely progress to high-risk disease, it was hypothesized that the ethnic disparities in neuroblastoma outcome could be due to genetic variation rather than social determinants. Gamazon and colleagues evaluated 13 single nucleotide polymorphisms (SNPs) known to be associated with high risk neuroblastoma and found that rs1033069 within sperm associated antigen 16 (SPAG16) was associated with high-risk disease and had higher risk allele frequency in the African population [2]. These findings support the concept that genomic variation may play a role in predicting outcome in children with neuroblastoma.

With additional patients added to the INRG Data Commons over the last decade, we aim to validate the findings that racial and ethnic disparities affect presentation and outcome in neuroblastoma.

**Significance:**
While there has been progress made in understanding the biologic features of neuroblastoma, as well as evolution of therapeutic strategies, approximately 25-30% of patients with high-risk disease will still experience recurrence despite intensive, multimodality therapy, and long-term survival for these children is dismal. This is in part due to the heterogeneity of the disease, therapy resistance, and toxicity. Continued understanding of the biological underpinnings of the disease as well as host factors, including racial and ethnic differences in presentation and response to therapy, will aid in
better risk stratification and selection of treatment for patients. This may help direct us to more effective, individualized treatment strategies for patients.

**Proposal Description:**
We will perform a detailed analysis of clinical, biological, and outcome (EFS, OS) differences between patients with neuroblastoma of differing racial and ethnic backgrounds enrolled on COG ANBL00B1. Race will be categorized as American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Asian, black or African American, or white. Ethnicity will be categorized as Hispanic/Latino or not Hispanic/Latino. A combined race/ethnicity variable will be created taking into consideration both the racial and ethnic backgrounds and coded as follows: non-Hispanic white, non-Hispanic black, Native American, Asian, and Hispanic.

We will evaluate any differences in patients’ demographics and clinical characteristics between the two cohorts using Chi-square tests and t-tests. For Aim 1, Chi-square tests (or t-tests when applicable) will be used to test for association of clinical characteristics (e.g., age), biological factors (e.g., MYCN status, ploidy), and risk group with racial/ethnic groups. For Aim 2, Kaplan-Meier curves will be generated to estimate EFS and OS for each racial/ethnic group. Log-rank tests will be used to compare survival curves across racial/ethnic groups. Similar analyses will be performed stratified according to risk group. Statistically significant factors (P < 0.05) from univariate analysis will be used to build Cox proportional hazards models to examine the association of demographic and clinical factors with EFS and OS and will be reported as hazard ratios with 95% CIs. For Aim 3, EFS will be calculated among black and white patients with high-risk disease with late events, which will be defined as first events that occur 2 years or later from diagnosis [1]. For this subgroup of patients, EFS will be calculated starting 2 years from diagnosis.

**Data Requested:** Patient characteristics, diagnostic information, outcomes, clinical trial and/or biology study enrollment and treatment arm, and all potential biologic risk factors for all patients treated on COG protocols for patients diagnosed between 2001 to 2016. As race and ethnicity data are essential to this proposal, we are restricting our data request to patients enrolled on a COG study.

Requested variables will include:
- Race
- Ethnicity
- Gender
- Age at diagnosis (to be analyzed as continuous variable and dichotomized as patients <18 months and ≥ 18 months)
- Stage at diagnosis (to be analyzed as categorical variables and also dichotomized as INSS stage 4 [or INRG stage M] vs. all others)
- Site of primary tumor
- Among patients with metastatic disease, sites of metastases
- Primary tumor size (maximum diameter; to be analyzed as continuous variable and possibly dichotomized above and below the group mean)
- Diagnostic category
- INPC prognostic group
- LDH at diagnosis (dichotomized at 587 U/L, per INRG standard)
- Ferritin at diagnosis (dichotomized at 92 ng/mL, per INRG standard)
- Urine catecholamines at diagnosis (positive vs. negative)
- MIBG avidity at diagnosis, if available
- Treatment/Treatment assignment
- Treatment era
Biologic Features
- MYCN status (amplified vs. non-amplified)
- DNA index/ploidy (diploid vs. hyperdiploid)
- LOH at 1p (present vs. absent)
- Gain of 17q (present vs. absent)
- 11q aberration (present vs. absent)
- Pooled segmental chromosomal aberration (LOH at 1p, gain 17q, and/or 11q aberration vs. none of these changes)
- MKI (dichotomized as high vs. low-intermediate)

Clinical Outcomes
- Time to first event (or last follow-up if no event)
- Time to first relapse (or last follow-up if no relapse)
- Time to death (or last follow-up if no death)

Collaborating Statistician: Sang Mee Lee, PhD

References