Associations between Tumor Ploidy and Overall Survival in Pediatric Neuroblastoma

Tyrel R. Porter, BS*; Emir Rinaldi-Pérez, MS*; Marcel Grau-Rodríguez, BS†; Lilia Y. Kucheryavykh, PhD*

Objective: To investigate the relationships between pediatric neuroblastoma outcomes, tumor ploidy, and ethnicity, focusing on disparities in overall survival (OS) while also accounting for race and ethnicity.

Methods: Clinical and tumor ploidy data for 63 Hispanic White, 561 non-Hispanic White, and 86 non-Hispanic Black patients were obtained from cBioPortal for Cancer Genomics (TARGET [Therapeutically Applicable Research to Generate Effective Treatments], 2018). Kaplan–Meier survival curves were analyzed using log-rank and Gehan–Breslow–Wilcoxon tests. Hazard ratios (HR) with 95% CIs were calculated using the Mantel–Haenszel method. Associations between ethnicity and tumor ploidy were assessed using the chi-square test.

Results: Significant differences in overall survival (OS) were observed between White patients who self-identified as Hispanic and those who identified as non-Hispanic, with Hispanic patients exhibiting worse outcomes. (P = .0076, HR = 1.907, 95% CI: 1.187–3.062). Median survival for Hispanic patients was 94 months but was undefined for non-Hispanic patients. Diploid tumors were associated with worse outcomes than hyperdiploid tumors were (P < .0001, HR = 2.291, 95% CI: 1.689–3.109). The chi-square test revealed a significant association between ethnicity and tumor ploidy (χ^2 = 4.220, P = .0400), with non-Hispanic patients having a higher proportion of hyperdiploid tumors (66.99%) than Hispanic patients (53.97%).

Conclusion: Hispanic White patients with neuroblastoma had lower OS than did non-Hispanic White patients, partly due to the former having a higher proportion of diploid tumors. These findings highlight the importance of considering ethnicity and tumor ploidy in risk stratification and treatment strategies.

[P R Health Sci J 2025;44(1):69-73]

Key words: Neuroblastoma, DNA ploidy, Pediatric

Neuroblastic tumors, which originate from neural crest cell derivatives in the sympathetic nervous system, pose a complex challenge in pediatric oncology (1). Neuroblastoma is the most common cancer in pediatric patients less than 1 year of age and does not commonly occur in adults (2,3). Despite advancements in therapies such as surgery and chemotherapy, neuroblastoma remains a significant pediatric cancer, accounting for 10% of all pediatric cancer cases and 15% of all cancer-related deaths in children (4).

Originating from the sympathetic nervous system, neuroblastoma can manifest in various extracranial locations throughout the body. However, approximately 65% of these tumors develop in the abdomen, with half of these cases involving the adrenal medulla (5). The tumor's location significantly influences the patient's clinical presentation, alongside factors such as tumor size and degree of invasion. These varied clinical presentations contribute to the numerous complications that may lead to the succumbing of pediatric patients to neuroblastoma.

Despite having diverse tumor locations and clinical presentations, pediatric neuroblastoma cases are widely assessed using the International Neuroblastoma Risk Group (INRG) classification system. (6). Stage, age, histological classification, tumor differentiation grade, *MYCN* oncogene status, and DNA ploidy are the most significant prognostic tools in this classification. More specifically, DNA ploidy, also known as tumor ploidy, serves as a method for evaluating the predominant chromosomal content in tumors, categorizing neuroblastoma tumors based on DNA index (DI) as diploid (DI = 1) or hyperdiploid (DI > 1). Hyperdiploid neuroblastoma tumors typically exhibit localized growth and a more favorable prognosis, while diploid tumors often harbor high-risk genetic abnormalities (7,8). Additionally, hyperdiploid neuroblastoma tumors have shown a better response to chemotherapy, which contributes to a decreased mortality rate (9).

In addition to the INRG classification, race and ethnicity have been implicated in risk-stratification (10,11). Genetic predispositions to cancer can vary significantly by ancestry, with some populations exhibiting a higher prevalence of certain pathogenic variants while others have lower rates of specific variants (12,13). These differences suggest that genetic predispositions to cancer can vary significantly by ancestry, which has implications for personalized cancer risk management. However, investigations

*Department of Biochemistry, †School of Medicine, Universidad Central del Caribe, Bayamón, Puerto Rico

The authors have no conflicts of interest to disclose.

Address correspondence to: Tyrel R. Porter, BS, Universidad Central del Caribe School of Medicine, Bayamón, PR 00956. Email: 122tporter@uccaribe.edu

into biological explanations for these disparities are limited. This paper aims to elucidate the relationship between neuroblastoma outcomes and the associated risk factor, DNA ploidy, and their relevance to ethnic disparities. By exploring the potential linkages between these variables, we seek to provide insights that may inform more targeted and equitable approaches to neuroblastoma management.

Methods

Clinical and tumor ploidy data, which included data on both race and ethnicity, were obtained for 63 Hispanic White patients, 561 non-Hispanic White patients, and 86 non-Hispanic Black patients from the cBioPortal for Cancer Genomics (Pediatric Neuroblastoma, Therapeutically Applicable Research to Generate Effective Treatments [TARGET], 2018) on November 14, 2024 (14–16). Neuroblastoma data obtained from all listed organ sites were included. Data were generated by TARGET (https://www.cancer.gov/ccg/research/genome-sequencing/target), dbGaP Sub-study ID phs000467, which began in 2007 and includes data collected (on an ongoing basis) for pediatric cancers.

Only a single sample per patient was included in the analysis to avoid redundancy and ensure the independence of the observations. Patients were excluded from the study if their clinical or ploidy data were incomplete or if their diagnosis did not meet the criteria for neuroblastoma. Additionally, cases with ambiguous or missing ethnicity designations were removed to ensure accurate subgroup comparisons.

To assess overall survival (OS) in relation to race, ethnicity, and tumor ploidy, several statistical methods were employed. The log-rank (Mantel–Cox) test, a method for comparing survival curves, evaluates whether there is a statistically significant difference between groups by comparing the observed and expected events over time. Additionally, the Gehan–Breslow–Wilcoxon test, which places more weight on earlier time points, was used to detect subtle differences in short-term survival outcomes not exposed by the log-rank test. Hazard ratios (HRs), along with 95% CIs, were calculated using the Mantel–Haenszel method to quantify the relative mortality risks associated with ethnicity and tumor ploidy, as this approach accounts for stratification and potential confounding factors, providing a more accurate estimate of risk across groups. The chi-square test of independence was employed to evaluate the relationship between ethnicity and chromosome ploidy. This test, suited for large sample sizes, assesses whether there is a significant association between 2 categorical variables by comparing observed and expected frequencies in a contingency table. All analyses were performed using GraphPad Prism 9.1.0 software.

This study, which utilized The Cancer Genome Atlas data, did not require Institutional Review Board approval.

Results

The OS analysis conducted on 5-year survival curves between Hispanic White and non-Hispanic White patients, using both log-rank and Gehan–Breslow–Wilcoxon tests, demonstrated significant differences (Table 1). The log-rank test yielded a chi-square value of 5.700 (P = .0170), while the Gehan–Breslow–Wilcoxon test had a chi-square value of 5.643 (P = .0175), both values suggesting better outcomes in non-Hispanic White patients. The median survival time for Hispanic White patients was 58 months, while the median survival for non-Hispanic White patients was undefined due to a lower mortality rate in the latter group. The Mantel–Haenszel HR was 1.759 (95% CI: 1.106–2.795) indicating a higher mortality risk for Hispanic White patients. The OS analysis of 5-year survival curves was insignificant for both the log-rank and Gehan–Breslow–Wilcoxon tests when comparing Hispanic White patients and non-Hispanic Black patients (P = .09 and .12, respectively) with an HR of 1.547 (95% CI: 0.9288–2.578).

To further investigate ethnic differences in OS, the analysis focused on the observed disparities in survival outcomes between Hispanic and non-Hispanic White patients. After identifying disparities in survival outcomes within the 5-year time frame, we expanded the analysis to include all the available OS data up to 167 months, aiming to better understand the observed ethnic differences (Figure 1a). The OS analysis comparing Hispanic and non-Hispanic White patients demonstrated significant differences in survival curves, as evidenced by the log-rank test (P = .0076, χ^2 = 7.134) and the Gehan–Breslow–Wilcoxon test (P = .0085, χ^2 = 6.935). The median survival time was 94 months for Hispanic patients and undefined for non-Hispanic patients. The Mantel–Haenszel HR for Hispanic patients compared to non-Hispanic individuals was 1.907 (95% CI: 1.187–3.062), indicating nearly a 2-fold increased risk of mortality in Hispanic patients.

A comparison of tumor ploidy 5-year survival curves in White patients, without accounting for ethnicity, revealed significant differences between diploid and hyperdiploid samples using both the log-rank and Gehan–Breslow–Wilcoxon tests (P < .0001 for both). The analysis demonstrated that diploid tumors were associated with worse outcomes, with lower survival rates compared to hyperdiploid tumors (Figure 1b). These results aligned with INRG classification, demonstrating a significant disparity in survival outcomes between White patients with diploid and hyperdiploid neuroblastoma tumors in the dataset used.

The chi-square test of independence was employed to assess the association between ethnicity and tumor ploidy in neuroblastoma patients (Figure 2). The analysis revealed a statistically significant relationship between Hispanic and non-Hispanic White patients (χ^2 = 4.220, P = .0400), indicating that ethnicity is associated with differences in tumor ploidy status. Among the Hispanic patients, 29 were classified as diploid and 34 as hyperdiploid, representing 46.03% and 53.97% of Hispanic patients, respectively. In contrast, the non-Hispanic patients comprised 172 diploid cases (33.01%) and 349 hyperdiploid cases (66.99%). These results suggest a higher proportion of hyperdiploid tumors in non-Hispanic patients compared to Hispanic patients.

Discussion

Our study supports the prognostic value of tumor ploidy for mortality rate (6). It also confirms the existence of pronounced ethnic disparities in survival rates and tumor ploidy in cases of pediatric neuroblastoma, particularly between Hispanic and

Table 1. Summary Table of Survival Rates, Hazard Ratios, and P Values Across Ethnic Groups

5-year Comparison	Test	Statistic/Chi-square Value	P Value	Survival Outcome	Hazard Ratio (95% CI)
Hispanic White vs. Non-Hispanic White	Log-Rank (Mantel–Cox)	5.7	.017	Higher mortality risk observed in Hispanic patients	-
	Gehan–Breslow–Wilcoxon	5.643	.0175	Higher mortality risk observed in Hispanic patients	-
	Mantel–Haenszel HR	-	-	-	1.759 (1.106–2.795)
	Median Survival	-	-	Hispanic: Median survival = 58 months; non-Hispanic: Median survival = Undefined	-
Hispanic White vs. Non-Hispanic Black	Log-Rank (Mantel–Cox)	2.81	.0937	No statistically significant difference in mortality risk	-
	Gehan–Breslow–Wilcoxon	2.468	.1162	No statistically significant difference in mortality risk	-
	Mantel–Haenszel HR	-	-	-	1.547 (0.9288–2.578)
	Median Survival	-	-	Black: Median survival = Undefined; Hispanic: Median survival = 58 months	-
Diploid vs. Hyperdiploid Tumors	Log-Rank (Mantel–Cox)	28.34	<.0001	Higher mortality risk observed in patients with diploid tumors	-
	Gehan–Breslow–Wilcoxon	25.45	<.0001	Higher mortality risk observed in patients with diploid tumors	-
	Mantel–Haenszel HR	-	-	-	2.291 (1.689–3.109)
	Median Survival	-	-	Diploid: Median survival = 63 months; Hyperdiploid: Median survival = Undefined	-

non-Hispanic populations (10,11). Importantly, our study also reveals that Hispanic patients demonstrated a higher prevalence of an accepted prognostic factor, diploid tumors, when compared to their non-Hispanic counterparts, which gives insight into the higher mortality rate.

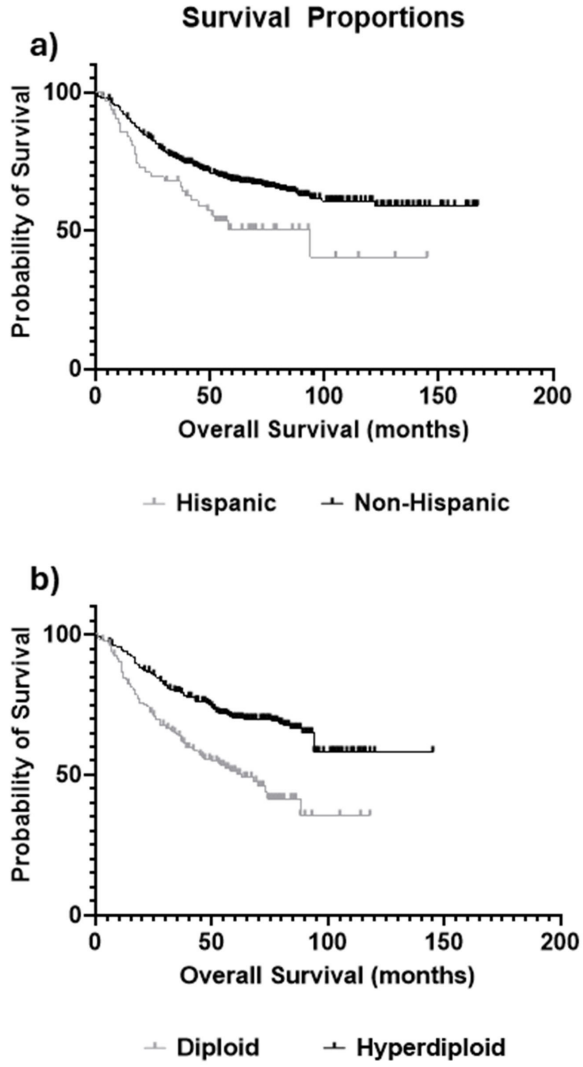
In addition to being a known prognostic indicator in neuroblastoma outcomes, diploid tumors are more predisposed to *MYCN* amplification compared to hyperdiploid tumors (7). *MYCN* amplification, as an additional prognostic indicator in neuroblastoma outcomes, is present in approximately 25% of neuroblastoma patients (17). This genetic aberration correlates strongly with a stark reduction in 5-year survival rates, which plummet to a mean of 50% in high-risk patients compared to approximately 90% to 85% in low- and intermediate-risk cohorts (18). Moreover, diploid tumors respond less favorably to treatment when *MYCN* amplification is also present (19). Given that diploid tumors may be predisposed to *MYCN* amplification and that their combined presentation in tumors reduces treatment effectiveness, it is plausible that *MYCN* amplification may play an additional role in the disparities observed in our research. However, more research delving into this additional prognostic factor and ethnic disparities is required. Furthermore, the exact numerical DI value for each tumor has been determined to be clinically pertinent, and the incorporation of these data in future research may elucidate our results (20).

The variations in cancer incidence, progression, and prognosis among different ethnic groups, particularly between Hispanic and non-Hispanic populations, are widely recognized but not fully understood (21). Previous research has revealed a heightened prevalence of high-risk neuroblastoma among Black patients, which aligns with the insignificant OS curves between White Hispanic and non-Hispanic Black patients observed in our results (22). Socioeconomic factors have been shown to have a substantial impact on health disparities and may account for some of the differences in mortality observed in our study (11,23). While our study focused on the biological underpinnings of neuroblastoma, the recognition of the interplay between these factors is relevant, as socioeconomic barriers might influence treatment outcomes.

The importance of this work extends beyond neuroblastoma, reflecting broader issues of ethnic disparities in cancer outcomes in the United States. Hispanic populations frequently face worse outcomes in several types of cancer, highlighting a critical need for health equity in medical research and treatment (21). Understanding and addressing the unique challenges faced by these communities is essential for improving health outcomes and ensuring that advancements in cancer treatment benefit all segments of the population equitably.

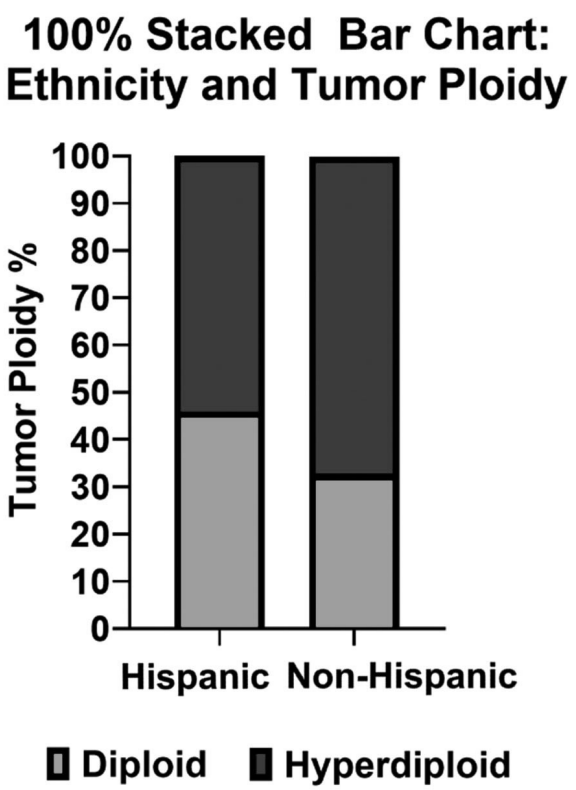
However, our study is limited by the smaller sample size of Hispanic White patients (n = 63), which may impact the

Figure 1. a) Kaplan–Meier survival curves consisting of White patients comparing Hispanic and non-Hispanic patients show significant differences in overall survival (OS) over 167 months. Statistical significance was observed in the log-rank test (P = .0076) and Gehan–Breslow–Wilcoxon test (P = .0085). The Mantel–Haenszel hazard ratio indicated increased mortality risk for Hispanic patients (HR = 1.907, 95% CI: 1.187–3.062). b) Compared to hyperdiploid tumors, diploid tumors in patients are associated with poorer 5-year survival, with both log-rank and Gehan–Breslow–Wilcoxon tests yielding P values less than .0001.



generalizability of the findings. Larger, more diverse cohorts are needed to confirm these results and to further investigate the biological and genetic underpinnings of these disparities. Future research could explore the potential role of *MYCN* amplification disparities in contributing to these outcomes, as the current literature has not extensively addressed this topic. Despite these limitations, our results emphasize the importance of considering ethnicity as a crucial factor in risk assessment and treatment planning for pediatric neuroblastoma patients.

Figure 2. A 100% stacked bar chart comparing categorical variables of ethnicity and tumor ploidy. The prevalence of diploid tumors in White patients was 46.03% in Hispanics and 33.01% in non-Hispanics. A chi-square test revealed significant associations ($\chi 2 = 4.220$, P = .0400).



Resumen

Objetivo: Este estudio examinó las diferencias en la supervivencia global (SG) entre no-hispanos blancos, no-hispanos afroamericanos, e hispanos blancos. Específicamente, este estudio analizó la relación entre la ploidía tumoral y la sobrevida de estos pacientes. Métodos: Datos clínicos sobre la ploidía tumoral fueron obtenidos de cBioPortal for Cancer Genomics (TARGET [por su abreviatura en inglés], 2018). Para propósitos de este estudio extrajimos los siguientes datos para nuestra población incluyendo 63 hispanos blancos, 561 no-hispanos blancos, 86 no-hispanos afroamericanos. Se realizaron curvas de supervivencia de Kaplan-Meier y pruebas de log-rank y Gehan-Breslow-Wilcoxon para comparar la SG entre grupos. Se calcularon las razones de riesgo (HR, por sus siglas en inglés) con intervalos de confianza (IC) del 95% utilizando el método Mantel-Haenszel. Se utilizó la prueba de chi-cuadrado para evaluar la asociación entre etnia y ploidía tumoral. Resultados: Se observaron diferencias significativas en la SG entre los pacientes hispanos y los no-hispanos blancos (p=0.0076, HR = 1.907, IC 95%: 1.187–3.062). La mediana de supervivencia para los pacientes hispanos fue de 94 meses, mientras que los pacientes no-hispanos blancos no alcanzaron la mediana de supervivencia. La SG también varió significativamente según la ploidía tumoral, siendo los

tumores diploides asociados con peores resultados en comparación con los tumores hiperdiploides (p<0.0001, HR = 2.291, IC 95%: 1.689–3.109). Además, se encontró una relación significativa entre la etnicidad y la ploidía tumoral (χ^2=4.220, p=0.0400), con el 53.97% de los tumores hiperdiploides en pacientes hispanos y el 66.99% en pacientes no hispanos.

Acknowledgments

Statement of Funding Sources: This study was supported by National Institutes of Health grants 1R15CA287203 and 1R16GM153522 and the Puerto Rico Science, Technology & Research Trust (2022).

References

1. Newman EA, Abdessalam S, Aldrink JH, et al. Update on neuroblastoma. J Pediatr Surg. 2019;54(3):383-389. doi:10.1016/j.jpedsurg.2018.09.004
2. Heck JE, Ritz B, Hung RJ, Hashibe M, Boffetta P. The epidemiology of neuroblastoma: a review. Paediatr Perinat Epidemiol. 2009;23(2):125-143. doi:10.1111/j.1365-3016.2008.00983.x
3. Franks LM, Bollen A, Seeger RC, Stram DO, Matthay KK. Neuroblastoma in adults and adolescents: an indolent course with poor survival. Cancer. 1997;79(10):2028-2035. doi:10.1002/(sici)1097-0142(19970515)79:10<2028::aid-cncr26>3.0.co;2-v
4. Swift CC, Eklund MJ, Kraveka JM, Alazraki AL. Updates in Diagnosis, Management, and Treatment of Neuroblastoma. Radiographics. 2018;38(2):566-580. doi:10.1148/rg.2018170132
5. Colon NC, Chung DH. Neuroblastoma. Adv Pediatr. 2011;58(1):297-311. doi:10.1016/j.yapd.2011.03.011
6. Cohn SL, Pearson AD, London WB, et al. The International Neuroblastoma Risk Group (INRG) classification system: an INRG Task Force report. J Clin Oncol. 2009;27(2):289-297. doi:10.1200/JCO.2008.16.6785
7. Schneiderman J, London WB, Brodeur GM, Castleberry RP, Look AT, Cohn SL. Clinical significance of MYCN amplification and ploidy in favorable-stage neuroblastoma: a report from the Children's Oncology Group. J Clin Oncol. 2008;26(6):913-918. doi:10.1200/JCO.2007.13.9493
8. Tomioka N, Kobayashi H, Kageyama H, et al. Chromosomes that show partial loss or gain in near-diploid tumors coincide with chromosomes that show whole loss or gain in near-triploid tumors: evidence suggesting the involvement of the same genes in the tumorigenesis of high- and low-risk neuroblastomas. Genes Chromosomes Cancer. 2003;36(2):139-150. doi:10.1002/gcc.10151
9. Baker DL, Schmidt ML, Cohn SL, et al.; Children's Oncology Group. Outcome after reduced chemotherapy for intermediate-risk neuroblastoma. N Engl J Med. 2010;363(14):1313-1323. doi:10.1056/NEJMoa1001527
10. Chennakesavalu M, Pudela C, Applebaum MA, et al. Persistence of Racial and Ethnic Disparities in Risk and Survival for Patients with Neuroblastoma over Two Decades. EJC Paediatr Oncol. 2023;2:100022. doi:10.1016/j.ejcped.2023.100022
11. Zheng DJ, Li A, Ma C, et al. Socioeconomic disparities in survival after high-risk neuroblastoma treatment with modern therapy. Pediatr Blood Cancer. 2021;68(10):e29127. doi:10.1002/pbc.29127
12. Yadav S, LaDuca H, Polley EC, et al. Racial and Ethnic Differences in Multigene Hereditary Cancer Panel Test Results for Women With Breast Cancer. J Natl Cancer Inst. 2021;113(10):1429-1433. doi:10.1093/jnci/djaa167
13. Seagle HM, Keller SR, Tavtigian SV, Horton C, Holowatyj AN. Clinical Multigene Panel Testing Identifies Racial and Ethnic Differences in Germline Pathogenic Variants Among Patients With Early-Onset Colorectal Cancer. J Clin Oncol. 2023;41(26):4279-4289. doi:10.1200/JCO.22.02378
14. Grossman RL, Heath AP, Ferretti V, et al. Toward a Shared Vision for Cancer Genomic Data. N Engl J Med. 2016;375(12):1109-1112. doi:10.1056/NEJMp1607591
15. Cerami E, Gao J, Dogrusoz U, et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data [published correction appears in Cancer Discov. 2012 Oct;2(10):960]. Cancer Discov. 2012;2(5):401-404. doi:10.1158/2159-8290.CD-12-0095
16. Gao J, Aksoy BA, Dogrusoz U, et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal. 2013;6(269):pl1. Published 2013 Apr 2. doi:10.1126/scisignal.2004088
17. Huang M, Weiss WA. Neuroblastoma and MYCN. Cold Spring Harb Perspect Med. 2013;3(10):a014415. Published 2013 Oct 1. doi:10.1101/cshperspect.a014415
18. Bartolucci D, Montemurro L, Raieli S, et al. MYCN Impact on High-Risk Neuroblastoma: From Diagnosis and Prognosis to Targeted Treatment. Cancers (Basel). 2022;14(18):4421. Published 2022 Sep 12. doi:10.3390/cancers14184421
19. George RE, London WB, Cohn SL, et al. Hyperdiploidy plus nonamplified MYCN confers a favorable prognosis in children 12 to 18 months old with disseminated neuroblastoma: a Pediatric Oncology Group study. J Clin Oncol. 2005;23(27):6466-6473. doi:10.1200/JCO.2005.05.582
20. Ambros PF, Ambros IM, Brodeur GM, et al. International consensus for neuroblastoma molecular diagnostics: report from the International Neuroblastoma Risk Group (INRG) Biology Committee. Br J Cancer. 2009;100(9):1471-1482. doi:10.1038/sj.bjc.6605014
21. Miller KD, Ortiz AP, Pinheiro PS, et al. Cancer statistics for the US Hispanic/Latino population, 2021. CA Cancer J Clin. 2021;71(6):466-487. doi:10.3322/caac.21695
22. Henderson TO, Bhatia S, Pinto N, et al. Racial and ethnic disparities in risk and survival in children with neuroblastoma: a Children's Oncology Group study. J Clin Oncol. 2011;29(1):76-82. doi:10.1200/JCO.2010.29.6103
23. Zheng DJ, Li A, Ma C, et al. Socioeconomic disparities in survival after high-risk neuroblastoma treatment with modern therapy. Pediatr Blood Cancer. 2021;68(10):e29127. doi:10.1002/pbc.29127