# Epidemiology and Molecular Determinants of Pediatric Osteosarcoma in an underserved population

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## ABSTRACT

Osteosarcoma (OS) presents a high incidence and rates of metastatic disease in Hispanic and African American pediatric patients. With the goal of understanding disparities within underrepresented communities affected by pediatric OS, we recently reported the epidemiology of pediatric OS within a Hispanic patient cohort. Malignant bone tumors represent 4.68% of all pediatric cancers in Hispanics living in Puerto Rico, with an age-adjusted incidence of 6.02 cases per million. Notably, 34.62% of these patients present localized disease while 42.3% have metastatic disease at diagnosis with a mortality rate of 2.4 per million. These statistics highlight the need for dedicated studies to address clinical and biological disparities in minorities.

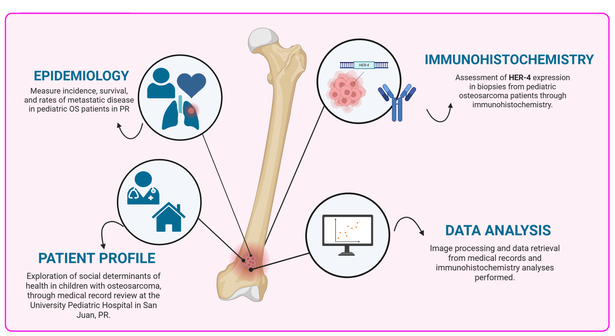
The Human Epidermal Growth Factor Receptor 4 (HER4), a member of the EGFR receptor family, is upregulated in pediatric OS patients with decreased overall survival. It regulates pathways for cell survival and proliferation and has been implicated in tumorigenesis in various cancers. Furthermore, the EGFR family can also modulate immune cell populations, although this is largely understudied in HER4 positive tumors including aggressive pediatric osteosarcoma.

The goal of our study is to evaluate HER4 expression in a cohort of Hispanic patients with pediatric osteosarcoma and determine whether HER4 expression can be predetermined by genetic ancestry. We hypothesize that underrepresented minorities including Hispanics and African Americans have higher HER4 expression, predisposing these patients to aggressive OS.

By retrospective medical record review between 2009-2023, we identified 45 patients between the ages of 1-19 years diagnosed with pediatric OS. 31 pediatric OS tissue blocks from biopsies, metastases, resections, and relapses were recovered from the Pathology Department of the Puerto Rico Medical Center. We performed immunohistochemistry (IHC) for HER-4 expression using a validated monoclonal HER4 antibody (Invitrogen). Our results show high HER-4 expression in most of our pediatric OS Hispanic patient cohort, suggesting that HER-4 may play drive a crucial step in OS tumor progression and metastasis within these communities. Ongoing analysis includes evaluating HER4 expression within Hispanics in US, Caucasians, and African Americans. Understanding how genetic ancestry can lead to disparities in pediatric OS has the potential to result in effective targeted therapeutic strategies for underserved minorities.

## HYPOTHESIS


## METHODOLOGY




## RESULTS

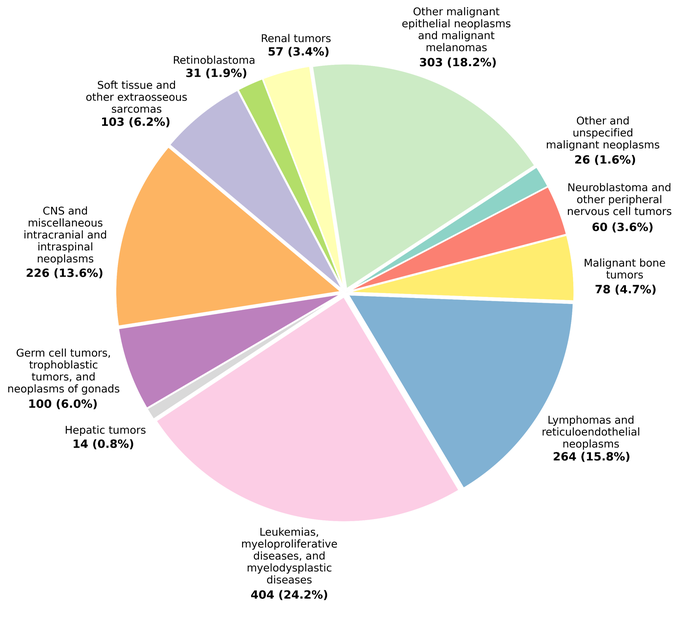
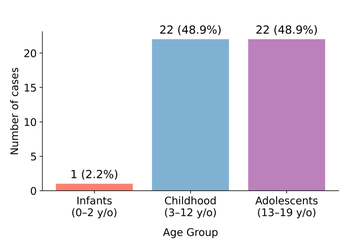
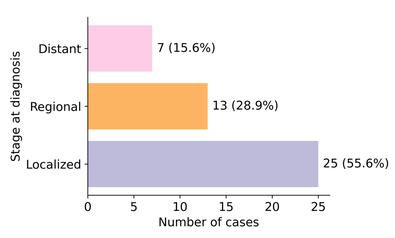



**Figure 1: Distribution of cancer types among children in Puerto Rico aged 0-19 years for the period 2009-2020, N=1666.** Data obtained from the Incidence Case file of Puerto Rico from the Puerto Rico Central Cancer Registry. Incidence counts and rates for 2017 are based on the first 6 months of reported data coupled with half the population estimate (January to June 2017). Data from July to December 2017 are excluded to account for the population shift that occurred due to Hurricane Maria.



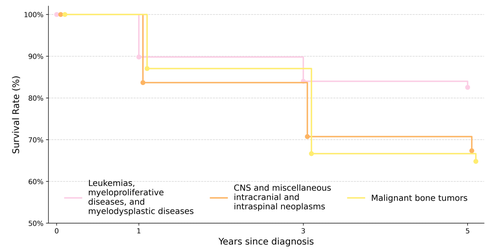
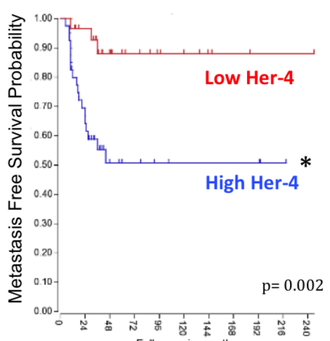





**Figure 2: Clinical profile of children diagnosed with osteosarcoma in Puerto Rico, from 2009-2024, N=45.** Geographic location, age distribution, stage at diagnosis and patient outcome as of December 31, 2024, is shown.
Kaplan-Meier survival curve comparing 5-year overall survival amongst children diagnosed with OS and other pediatric cancers in Puerto Rico.



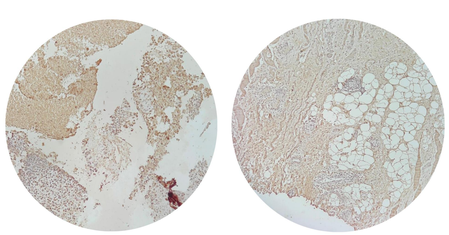



**Figure 3: Increased HER-4 expression in OS patients in Puerto Rico.** HER-4 expression in pediatric OS has been previously described to correlate with lower survival (K-M survival curve to the left generated from the Kuijjer dataset using the R2 Genomics Analysis and Visualization Platform). Representative images at 10X magnification for 2 diagnostic biopsies from patients with OS shows increased HER-4 expression via IHC.

## DISCUSSION

- Although pediatric osteosarcoma presents higher incidence and higher rates of metastatic disease in minority groups like Hispanics and Blacks, studies are lacking to better characterize these disparities.
- Our study shows that in Puerto Rico, the most frequent cancer types diagnosed in children are leukemia, malignant epithelial neoplasms and lymphomas.
- Malignant bone tumors including pediatric osteosarcoma, comprise 4.7% of all pediatric cancer diagnoses in Puerto Rico.
- During the period from 2009-2020, close to 45% of patients diagnosed with pediatric osteosarcoma in Puerto Rico presented metastatic disease at diagnosis.
- Together, the central and southeast regions of PR have most pediatric osteosarcoma cases and ages are evenly distributed between children and adolescents.
- Survival at 5 years for this patient cohort is close to 65% which is slightly lower than the US average of 70%.
- Initial studies demonstrate higher HER-4 expression in OS biopsies from patients in Puerto Rico.
- Future studies in our lab will focus on understanding the social determinants of health including timely access to care, time from initial symptom to diagnosis and start of therapy, insurance among others as potential disparities.
- Furthermore, we intend to explore differences in genetic background in patients from Puerto Rico and how this contributes to pediatric osteosarcoma progression.

## ACKNOWLEDGEMENTS

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