Background: Chordomas are rare aggressive primary bone cancers affecting the skull-base and spine. Despite standard of care treatment with radical surgical resection and radiotherapy, the overall survival at 10 years is only 40%, with most patients experiencing disease recurrence. We have previously identified robust DNA methylation-based prognostic subtypes of chordomas, a poorer performing Immune infiltrated subtype and a better performing Cellular subtype. Here we have aimed to further characterize these prognostic subtypes with an extensively annotated clinical database to identify factors that correlate with each subtype.

Methods: 68 patients from a multi-institutional 20-year series were identified. These patients' tumor samples had undergone whole genome DNA methylation profiling on the Illumina EPIC array. Baseline clinical features, including clinical features (age, sex, pain or neurological deficit at presentation, tumor size & diameter, tumor location), treatment details (extent of resection, complications, histological subtype, adjuvant radiotherapy), outcomes parameters (recurrence, metastasis, status of disease control) and imaging parameters (dural invasion, vascularity, soft-tissue extension, bony desctruction) were analyzed using chi-squared or kruskal-wallis test.

Results: Of all the variables tested, age of onset (p-value 0.012), location (skull base vs spine vs sacral: p-value 0.0365) and histological subtype (classical vs chondroid: p-value 0.0132) were the only significant predictors of subgroup placement; older age, spinal location, and classical histological typing were predictors of immune infiltrated chordoma subtype, which has a poorer clinical performance. As expected, death from chordoma was significantly different between subtypes (p-value 0.0056). Notably, imaging characteristics of the tumor did not correlate with subtype.

Conclusion Overall, there are limited variables that correlate with methylation subtype after thorough assessment of clinical factors, meaning that the newly identified epigenetic chordoma subtypes cannot be reliably identified using clinical or imaging features of the patient and their tumor alone in the absence of molecular data.