The Children’s Oncology Group (COG) and Curesearch recognized that many samples in the biorepository lacked clinically linked data, and the overall value of the repository was diminished. Additionally there was no biostatistical support available to basic and translational projects from the osteosarcoma repository that stagnated their publication. To address these problems the Childhood Sarcoma Biostatistics and Annotation Office (CSBAO) was created to provide the following information:

1. Management of clinical annotation for all patient samples held in the osteosarcoma repository (including validation of clinical annotation quality and completeness).

2. Review and aid in completion of statistical technical reports for biology and other osteosarcoma-related projects.

3. Development of a standard operating procedure (SOP) for collecting quality specimens for AOST0801.

The CSBAO worked with all of the treating institutions that had patients lacking clinically annotated data in order to recover critical information.

Results: P9851 was open for 3218 days (8.82 years), which should yield 3258 expected cases of pediatric osteosarcoma. P9851 collected samples from 1105 patients (or 31% of the expected cases of pediatric osteosarcoma). At the time of last data freeze and analysis AOST0801 has been open for 1595 days (4.34 years) which yields 2120 expected cases. So far it has enrolled 621 patients with osteosarcoma or 29.5% of the expected pediatric osteosarcoma population.

27 research projects have been completed using samples from P9851 and AOST0801, of these 23 have published in peer reviewed journals. Additionally, one of the successes of the CSBAO has been to help move 7 osteosarcoma biology projects into publication by providing biostatistical support (Table 1).

1. Management of clinical annotation for all patient samples held in the osteosarcoma repository (including validation of clinical annotation quality and completeness). As a result of efforts of the CSBAO, 90.8% these patient samples are now linked to clinical annotation.

2. Review and aid in completion of statistical technical reports for biology and other osteosarcoma-related projects. The CSBAO has worked with all of the treating institutions that had patients lacking clinically annotated data in order to recover critical information.

3. Development of a standard operating procedure (SOP) for collecting quality specimens for AOST0801. The CSBAO has provided the following information in order to recover critical information:

- Background: Osteosarcoma represents a common malignant bone tumor diagnosed in children. There are about 400 new pediatric and adolescent patients with this diagnosis per year in the US. Current treatment that provides patients with the greatest opportunity for survival osteosarcoma involves multidisciplinary treatment including surgery, chemotherapy, and radiation. The chemotherapy regimens used are long and intensive including cisplatin, doxorubicin, and high dose methotrexate with or without ifosfamide, and etoposide. These agents have a high incidence of acute and late side effects including cardiotoxicity, hearing loss, decreased fertility, and development of a secondary malignancy.

- Methods: Our project was designed to increase the understanding of what genetic drivers play a part in osteosarcoma oncogenesis in relation to other sarcomas. Unlike Ewing Sarcoma, the most common bone tumor in children, which has a balanced karyotype with the uniform reciprocal translocation (EWS/FLI1), osteosarcoma appears to be a much more heterogeneous disease with complex karyotypes. [4] The known genetic mutations associated with osteosarcoma include the P53 gene associated with Li Fraumeni Syndrome, the Rb1 tumor suppressor gene associated with hereditary retinoblastoma, BLM gene seen in Bloom syndrome, and RECG1 gene associated with Rothmund Thomson syndrome. In this age of personalised medicine we need to understand the genetic mechanisms of osteosarcoma to develop drugable targets, overcome resistance to therapy, and prognostic and risk stratify pediatric patient treatments.

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- Conclusions: As a result of the COG, QuadW foundation and the CSBAO efforts of the two osteosarcoma banking efforts, a total of 1708 patients with osteosarcoma samples with clinically linked data has been collected.

- The value the COG Osteosarcoma Biopspecmen Repository has been increased significantly by the efforts of the CSBAO by obtaining missing clinical annotation.

- Our goal is to continue to high quality samples of tumor and related tissue samples as well as biostatistical support to qualified researchers with projects that advance the understanding and treatment of patients with osteosarcoma.

- A future direction for the COG Osteosarcoma Biopspecimen Repository will be to link biological data generated by investigators to the physical and clinical data for banked samples.

Fig 1. Patient accrual to the Osteosarcoma Biology studies (P9851 and ASOT 0681) has proceeded at or above expectations.

Fig 2. Successful clinically annotation for the majority of patients represented in the osteosarcoma biopspecimen repository. A substantial limitation to the use of this biopspecimen repository was that only 5.3% of samples from patients not enrolled in clinical trials had overall clinical annotation. As a result of efforts of the CSBAO, 90.8% these patient samples are now linked to clinical annotation.

Fig 3. Sample of tissue microarrays that are available to researchers. There are 52 patient sample on the array as well as 10 healthy tissues (adrenal, renal, and testis) as controls. 38 of the 52 samples have clinically annotated data available. One of the patients on the array had osteosarcoma following treatment for acute leukemia and is considered a secondary malignancy.

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- We have begun to collect this data into a High Dimensional Database (HDD) that will be available for qualified researchers to conduct in silico studies.

- Eventually we expect the HDD to contain information including: EMB-2, Chromosomal Instability, Tenesorre, Factors Expression, 1000 gene expression assays and SPECS gene expression data, genome wide association study data, and array data from the TARGT project.

- The next direction the CSBAO will take is to expand its efforts to aid in other childhood sarcomas, most recently Ewing sarcoma and soft tissue sarcoma including rhabdomyosarcoma.