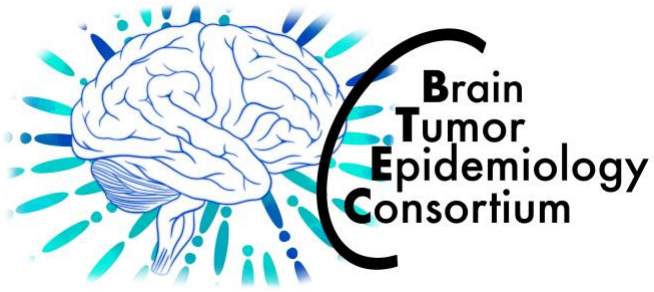

BTEC 2023 Annual Conference

Impact of Environment on Pediatric and Adult Brain Tumors

Abstracts

Health-related Quality of Life after Surgery for Lower Grade Gliomas

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Background: Limited data exist on long-term quality of life (QOL) for adults diagnosed with lower grade glioma.

Materials and Methods: The data are on 320 persons with adult lower grade (World Health Organization grade 2/3) glioma enrolled in the International Low Grade Glioma Registry. Data on QOL was collected using the Medical Outcomes Study 36-Item Short Form Health Survey (MOS SF-36); data on symptoms were also collected. QOL outcomes were examined by LGG treatment group and also compared to those of a population-based case/control study of meningioma (the Meningioma Consortium). In that study, 1722 meningioma cases diagnosed among residents of Connecticut, Massachusetts, California, Texas, and North Carolina from May 1, 2006 through March 14, 2013 were enrolled and frequency matched to 1622 controls by age, sex, and geography.

Results: The LGG sample average age is 45 years at time of interview and 53.1% male. 54.7% of patients had received radiation and chemotherapy (primarily temozolomide), 32.4% had received neither. Almost two thirds of LGG patients report difficulty with speaking and memory and over 1/3 (39%) of patients report some personality change. Fourteen percent report ongoing seizures and 34.1% report difficulty with driving an automobile. After controlling for age, education level, and other co-morbidities, patients diagnosed with LGG report levels of physical, emotional, and mental health functioning below those reported by meningioma patients as well as a general healthy population.

Conclusions: Despite being relatively young, persons with LGG report statistically significant decreases in quality of life compared to persons with non-malignant brain tumors and to a control population, highlighting the need to better acknowledge and manage these symptoms for this group of patients diagnosed in the prime of life.

Subsequent CNS Malignancy Among Survivors of Childhood Cancer: a Report from the Childhood Cancer Survivor Study (CCSS)

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Background: Subsequent malignant neoplasms (SMNs) of the central nervous system (CNS) following childhood cancer are a frequently fatal late effect of cancer therapy.

Materials and Methods: We used the CCSS (5-year childhood cancer survivors, diagnosed 1970-1999) to assess whether temporal changes in therapy have reduced CNS SMN risk. Twenty-year cumulative incidence rates (95% confidence interval) were estimated, and standardized incidence ratios (SIR, 95% CI) were calculated comparing observed to expected rates from SEER. Multivariable models assessed demographic and treatment-related risk factors for CNS SMN.

Results: Among survivors diagnosed between 1970-1979 (N=6223), 1980-1989 (N=9680), and 1990–1999 (N=8999) with median follow-up of 40.5, 32.2, and 22.6 years, respectively, 157 CNS SMNs (1970s, 52; 1980s, 63; 1990s, 42) were identified, excluding meningiomas. Malignant gliomas (N=131) were the most common SMNs. Cranial radiotherapy (CRT) exposure decreased by treatment decade, with the proportion of survivors receiving no CRT increasing from 23.0% (1970s), to 45.7% (1980s), and 66% (1990s). Decreases in >0–10Gy exposure (39.0% to 14.1%) and 20.1–30Gy (19.2% to 2.4%) were observed while those receiving >30Gy CRT has not substantially changed (12%, 11.1%, and 8.8%, respectively). Twenty-year cumulative incidence and SIR for development of SMN were 0.32% (0.18-0.46%) and 6.6 (5.0–8.7); 0.55% (0.41-0.70%) and 8.3 (6.6-10.4); and 0.43% (0.31-0.55%) and 9.2 (7.0–12.0), respectively, with no statistically significant differences between treatment eras, including when stratified by attained age. Multivariate analysis showed increased risk for all CRT dose levels >10Gy and for primary diagnoses of medulloblastoma/PNET (HR 3.6, 2.0-6.6) and astrocytoma (HR 2.4, 1.4-3.9). Three-year cumulative incidences of death after SMN, by treatment decade, were 70%, 73%, and 69%, respectively.

Conclusions: In conclusion, CNS SMN incidence has not decreased despite fewer survivors being treated with CRT, and CNS SMNs remain a significant source of mortality for affected patients.

Immune Profiles of Lower Grade Adult Glioma Patients

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Background:

Although immunosuppression is a known characteristic of glioma, there is little known about the peripheral immune status of lower grade glioma patients throughout the course of their disease. In this study, we examine immune profiles of glioma patients presurgery and other clinically relevant time points.

Materials and Methods:

Using immunomethylomic, (deconvoluted blood DNA methylation), data from the UCSF Adult Glioma and Immune Profiles Studies (AGS and IPS), we examine patient peripheral blood immune cell profiles in relation to survival in AGS patients and explore changes in new and recurrent lower grade glioma IPS patients, pre-surgery, post-surgery, and at clinically relevant time points. For patients receiving radiation and temozolomide (n=75), blood also is collected at progression MRI, pre-RT/TMZ, post-RT/TMZ, and before, during, and after adjuvant TMZ (if applicable). For patients being followed only by MRI (n=53) and those with other or variable treatment plans (n=67), blood also is collected at MRIs, and if applicable prior to radiation.

Results:

Preliminary results suggest that compared to controls, oligodendroglioma patients may have significantly different proportions of several immune cell types based on an extended library of immune subsets (e.g., B-memory cells, B-naïve cells, neutrophils, t-regulatory cells). We have further shown that age and immune cell types may stratify survival times for lower grade glioma patients (Molinaro et al. 2022), that dexamethasone taken at time of blood draw confounds associations of glioma subtypes with immune cell fractions (Bracci et al., 2022), and that the Neutrophil Dexamethasone Methylation Index, a measure of patient response to dexamethasone, predict survival after controlling for other important clinical variables (Wiencke et al. 2022).

Conclusions:

These and other preliminary results suggest the importance of detailed knowledge about glioma patient immune status and dexamethasone response.

Association between Living Near Oil and Gas Wells and Mortality in Children with Brain Tumors

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Background: Environmental pollutants can adversely affect children, but their impact on survival of childhood brain tumors (CBTs) is largely unknown. Oil and gas wells are linked to several chemicals, including carcinogens. We examined whether living near oil and gas wells is associated with mortality in children with brain tumors.

Materials and Methods: This study included children with a primary diagnosis of a malignant brain tumor by age 19 in the Texas Cancer Registry, 1995-2017. The location of oil and gas wells in Texas was obtained from the Texas Railroad Commission, the state agency that regulates this industry. Wells were categorized as 1) oil or gas well, 2) service, storage, injection, or disposal well, 3) permitted wells, 4) horizontal drainholes, or 5) sidetrack well. Residential address at diagnosis was geocoded and distance to oil and gas wells in Texas was calculated to determine whether a well was located within 1000m from the child's home (yes/no). We conducted Cox regression with each well category, adjusting for sex, census tract-level poverty, race/ethnicity, age at diagnosis, and decade patient was diagnosed. Analyses were repeated by CBT subtypes (e.g., astrocytoma, medulloblastoma, ependymoma, PNET, and other gliomas).

Results: 5,172 children were diagnosed with a brain tumor, of which 1,554 (30%) had a recorded death. The 5-year overall survival was 73%. 351 (6.8%) live within 1000m of an oil or gas well. Across the five well types, living within 1000m of a well was not associated with CBT survival. In tumor-specific analyses, living within 1000m of service, storage, injection, or disposal wells elevated mortality of astrocytoma (HR: 2.30, 95% CI: 0.76, 2.21) and ependymoma (HR: 2.04, 95% CI: 0.64, 6.54). Living within 1000m of horizontal drainholes increased death in medulloblastoma (HR: 1.31, 95% CI: 0.82, 2.10). Living within 1000m of sidetrack wells increased mortality of ependymoma (HR: 1.27, 95% CI: 0.68, 2.38).

Conclusions: Residential proximity to certain oil and gas wells may increase risk of mortality in specific CBT subtypes, providing preliminary evidence that environmental pollutants may contribute to overall survival.

Descriptive and Clinical Epidemiology of Intracranial Solitary Fibrous Tumor in France

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With the participation of the Association Picarde pour l'Optimisation des Thérapeutiques Anti-Cancéreuses (APOTAC), the French Brain Tumor DataBase (FBTDB), the Club de Neuro-Oncologie de la Société Française de Neurochirurgie (CNO-SFNC), the French Neuropathology Network (RENOCLIP-LOC) and the Association des Neuro-Oncologues d'Expression Française (ANOCEF)

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Background:

Intracranial solitary fibrous tumor (SFT) (including hemangiopericytoma-HPC- since the 2016 WHO classification) is a rare primary tumor of the central nervous system (CNS), and its epidemiology is poorly known. In this study, we aimed at providing descriptive epidemiological, clinical and therapeutic data of CNS-SFT.

Materials and Methods:

Firstly, we collected the data from the "French Brain Tumor DataBase" (FBTDB) cases and analyzed the incidence, sex-ratio, median age of all newly diagnosed and histologically confirmed SFT and HPC of the CNS, in France, between 2006 and 2015. Secondly, clinical, pathological and therapeutic records of adult patients were retrospectively reviewed to extract the relevant clinical factors for intracranial cases with sufficient information at 16 French centers.

Results:

Between 2006 and 2015, 399 incident cases of newly diagnosed and histologically confirmed SFT (including HPC) of the CNS were recorded. The number of female was 223/399 and median age at diagnosis was 55 years. The crude rate was 0.063 per 100,000 persons per year. The age-standardized incidence rates (World/Europe/USA standard population) were 0.045/0.059/0.056 per 100,000 persons per year, respectively.

The retrospective clinical study included 88 patients (female 50/88, median age at diagnosis 54.5 years [range: 19-88], median follow-up 7 years) in the sixteen participating French centers. The WHO histoprognostic grades were grade 1, 2, 3 or not defined for 1, 25, 51 and 11 patients, respectively. Eight patients received preoperative embolization. Gross tumor resection (GTR), subtotal resection (STR), resection not otherwise specified and biopsy were performed in 75, 9, 3 and 1 cases, respectively. After initial surgery, 32 patients received adjuvant radiotherapy.

The median overall survival (OS), progression-free survival (PFS), and local recurrence-free survival (LRFS) were 13 years, 7 years, and 7 years, respectively. Forty-two patients experienced recurrence. Extra cranial metastasis occurred in 16 patients. Median OS and PFS after the first recurrence were 6 years and 15.4 months, respectively.

Age and midline tumor topography were associated with poorer OS. A higher histological grade was a prognosis factor for PFS ($p = 0.04$) and LRFS ($p = 0.03$). GTR influenced LRFS ($p = 0.03$).

Conclusions:

In our nationwide study, crude rate and age-standardized incidence rate (reference population: world) of SFT (including HP) were 0.063 and 0.045 per 100,000 persons per year, respectively. For 88 patients with

intracranial SFT and sufficient data, GTR provided benefits as a first-line treatment. However, approximately 40% of patients experienced relapse. SFT remains a therapeutic challenge.

The association between Medicaid enrollment continuity and childhood, adolescent, and young adult brain tumor survival

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Background: Disparities in childhood, adolescent, and young adult cancer survival between individuals with Medicaid and private insurance have been reported. To further understand the association between insurance-related access to healthcare and brain tumor survival in this age group, we used Surveillance, Epidemiology, and End Results (SEER)-Medicaid-linked data to test two hypotheses: 1) those linked to Medicaid have lower brain tumor survival than those not linked, and 2) those with discontinuous enrollment in Medicaid around the time of diagnosis have lower survival than those with continuous enrollment.

Materials and Methods: SEER-Medicaid linked data from 2006 to 2013 were obtained. Follow-up for vital status was through 2018. We included individuals diagnosed with a first malignant primary brain cancer between 0 to 39 years. We excluded individuals who were linked to Medicaid enrollment records in multiple states during the same year. Individuals were defined as Medicaid-linked if they were linked to Medicaid in any U.S. state or the District of Columbia from 2006 to 2013. Medicaid enrollment was classified as continuous (enrolled within both the three months before and after diagnosis) and discontinuous (enrolled only within the three months before or after diagnosis or only at diagnosis). We used Kaplan-Meier (KM) curves and Cox Proportional Hazards (PH) regression models to evaluate survival differences in association with Medicaid linkage and enrollment timing after adjusting for age, race, and a measure of census tract poverty.

Results: Our analytic dataset included 10,586 children, adolescents, and young adults, among which there were 3,352 brain tumor deaths. Consistently lower survival probabilities over time in both children and adolescents ages 0 to 19 years and young adults ages 20 to 39 years were observed for those who linked to Medicaid compared to those who did not link to Medicaid ($p < .0001$). Those who were linked to Medicaid who were 0 to 19 and 20 to 39 years old at diagnosis had 1.63 (95% CI 1.47-1.82) and 1.46 (95% CI 1.33-1.60) times higher hazards of death vs. those who did not link, respectively. Among both age groups, higher hazards of death were observed in those with continuous (HR_{0-19} =1.59, 95% CI 1.40-1.82; HR_{20-39}=1.13, 95% CI 0.98-1.32) and discontinuous (HR_{0-19} =2.18, 95% CI 1.80-2.65; HR_{20-39}=2.07, 95% CI 1.80-2.37) Medicaid enrollment vs. those not linked to Medicaid. Similar patterns were consistently observed for specific brain tumor types for each age group in association with Medicaid linkage.

Conclusions: These results indicate an insurance-associated disparity in a national sample of younger brain tumor patients and provide information on risks in association with Medicaid enrollment continuity with the highest risks for death for those with discontinuous enrollment. These results further support the critical need for consistent health insurance coverage in children, adolescents, and young adults and for additional research to understand social, economic, and access-related factors leading to lower survival in the Medicaid population. Lowering administrative burdens for Medicaid enrollment, eligibility, and renewal are potentially important strategies for improving cancer outcomes.

Interactive Effects of Molecular, Therapeutic, and Patient Factors on Outcome of Diffuse Low-Grade Glioma

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*****Presenting author

Background: In patients with diffuse low-grade glioma (LGG), the extent of surgical tumor resection (EOR) has a controversial role, in part because a randomized clinical trial with different levels of EOR is not feasible.

Materials and Methods: In a 20-year retrospective cohort of 392 patients with IDH-mutant grade 2 glioma, we analyzed the combined effects of volumetric EOR, molecular and clinical factors on overall survival (OS) and progression-free survival by recursive partitioning (RPA). The OS results were validated in two external cohorts (n=365). Propensity score analysis of the combined cohorts (n=757) was used to mimic a randomized clinical trial with varying levels of EOR.

Results: RPA identified three survival risk groups. Median OS was shortest in two subsets of astrocytoma patients: those with post-operative tumor volume (TV) >4.6 mL; and, those with pre-operative TV >43.1 mL and post-operative TV ≤4.6 mL. Intermediate OS was seen in astrocytoma patients who had chemotherapy with pre-operative TV ≤43.1 mL and post-operative TV ≤4.6 mL in addition to oligodendroglioma patients with either pre-operative TV >43.1 mL and residual TV ≤4.6 mL or post-operative residual volume >4.6 mL. Longest OS was seen in astrocytoma patients with pre-operative TV ≤43.1 mL and post-operative TV ≤4.6 mL who received no chemotherapy and oligodendroglioma patients with pre-operative TV ≤43.1 mL and post-operative TV ≤4.6 mL. EOR ≥75% improved survival outcomes, as shown by propensity score analysis.

Conclusions: Across both subtypes of LGG, EOR beginning at 75% improves OS while beginning at 80% improves PFS. Nonetheless, maximal resection with preservation of neurological function remains the treatment goal. Our findings have implications for surgical strategies for low-grade gliomas, particularly oligodendroglioma.

Geospatial analysis of pediatric brain tumors in Kentucky, 1995-2019

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Background:

Pediatric brain tumors (PBTs) account for a large share of cancer-related morbidity and mortality among children in the United States, but their etiology is not well understood. As with several cancers, the Appalachian region of Kentucky has been shown to have high rates of PBTs.

Materials and Methods:

This study explored PBT incidence over 25 years in Kentucky at the population level to identify geographic and temporal trends and generate hypotheses for future research. The Kentucky Cancer Registry contributed data on all PBT diagnosed in Kentucky among those aged 0-29 during years 1995-2019. County-level age- and sex-adjusted spatio-temporal scan statistics—stratified by type of PBT and for all types combined—comprised the primary analysis. These results were mapped along with county-level environmental and occupational data.

Results:

High rates of rare astrocytomas were clustered in a north-south strip of central Kentucky toward the end of the study period, while high rates of other types were significantly clustered in eastern and western Kentucky. The area where some of these clusters overlapped, in north-central Kentucky, had significantly higher rates of PBTs generally. This region is home to some of Kentucky's signature industries, including horse farming and bourbon distilling.

Conclusions:

Some types of PBT appear to be more common in relatively urban and affluent regions, while others are more common in eastern Kentucky. The overall incidence of PBT appears to be increasing in Kentucky, as most clusters were recent. Additional population-based, observational studies could generate additional hypotheses. Individual-level studies should explore parents' occupational and children's household environmental exposures.

Obesogenic diet exposure increases pediatric brain tumor formation, partly through effects of maternal exposure on the tumor cell of origin

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Background: Pediatric low-grade glioma incidence has been rising in the U.S. over the last 20 years, concurrent with a rising rate of obesity in both the adult and pediatric populations. Recently, children of obese mothers have been demonstrated to have increased rates of several tumors, including brain tumors. Importantly, obesity in the U.S. is driven in large part by diet, given the abundance and accessibility of high-fat, high-sugar food choices. High-fat diet exposure has been previously demonstrated to promote proliferation and glial differentiation of neuroglial progenitor cells (NPCs) around the third ventricular zone (TVZ), suggesting that *in utero* exposure to an obesogenic diet might affect the formation of pediatric tumors derived from these cells, such as Neurofibromatosis Type 1 (NF1)-related optic pathway glioma (OPG). Based on these data, we hypothesized that maternal obesogenic exposure would increase *Nf1*-OPG formation through intrinsic effects on the tumor cell of origin.

Materials and Methods: We utilized a series of *Nf1*-heterozygous and *Nf1*-OPG mouse models for these experiments. We exposed dams and offspring to an obesogenic high-fat, high-sucrose diet to mimic dietary conditions prevalent in the U.S., with control chow-exposed animals as a comparison. Fetal brains from mothers exposed to different dietary conditions were analysed at E19. For tumor development studies, offspring were continued on their respective maternal diets and optic nerves analyzed for tumor formation at 6w-3mo.

Results: We demonstrated that progeny from obese dams exposed to an obesogenic diet demonstrated increased proliferation and glial differentiation of WT and *Nf1*-heterozygous TVZ NPCs *in vivo*. We found that this effect was due to diet rather than weight, as progeny of non-obese dams exposed to this diet only during gestation demonstrated a similar phenotype, and offspring of overweight dams switched to control chow at mating did not. We then assessed how obesogenic diet exposure affected tumor formation. We determined that this exposure increases glioma penetrance in two low-penetrance models of *Nf1*-OPG. Finally, we demonstrated that obesogenic diet exposure resulted in earlier tumor onset in a high-penetrance *Nf1*-OPG model.

Conclusions: Taken together, these findings demonstrate that obesogenic diet exposure increases pediatric glioma formation in this region of the brain, and suggest that this might occur in part through effects on the tumor cell of origin while still *in utero*. It may also have implications for clinical prognosis, as earlier age of tumor onset has been negatively associated with visual outcomes in NF1-OPG.

Association between exposure to air pollution and brain tumor incidence in the United States

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Background: Air pollution contains known carcinogens as well as compounds that impact brain health. Studies evaluating an association between exposure to pollution and brain and other central nervous system tumor (BT) risk have been inconclusive. We investigated the association between exposure to air pollution and incidence of BT in the United States (US) in an ecological study.

Materials and Methods: Annual county-level air pollution from 2000-2015 was obtained from the Environmental Protection Agency's Air Quality Index (AQI), which analyzes daily ambient air concentration for ozone and particulate pollution for selected counties in the US and describes the air quality as good, moderate, unhealthy for sensitive populations, unhealthy, very unhealthy, or hazardous. The mean number of annual unhealthy days was calculated and divided into tertiles of high, median, and low pollution levels. Counties with unknown AQI were excluded, as well as Nevada years 2018-2019, and Kansas and Minnesota for all years. County-level BT incidence between 2004-2019 was estimated using data from the Central Brain Tumor Registry of the United States, which aggregates BT data from the Centers for Disease Control and Prevention's National Program of Cancer Registries and the National Cancer Institute's Surveillance, Epidemiology, and End Results Program. Annual age-adjusted incidence rates (AAAIRs) were generated for each AQI tertile and further stratified by tumor behavior (malignant vs non-malignant), age group at diagnosis, sex, race/ethnicity, and county urbanicity. Incidence rate ratios (IRR) and 95% confidence intervals (95%CI) were calculated to evaluate significant differences (α=0.05).

Results: There were 1,177 counties with available data representing ~80% of the US population. Overall, low-pollution counties had lower AAAIR of BT compared to high-pollution counties (IRR=0.94, 95%CI: 0.94-0.95). This association was consistent when stratified by tumor behavior (malignant IRR=0.99, 95%CI: 0.97-1.00; non-malignant IRR=0.92, 95%CI: 0.92-0.93). Low-pollution counties had significantly lower AAAIR among those 40+ years overall and by behavior. This age group also had higher AAAIR than all other age groups. When stratified by sex and county urbanicity, low-pollution counties had lower AAAIR overall and by behavior in all groups compared to those in high-pollution counties except those in nonmetropolitan counties with malignant behavior. Low pollution was associated with a higher AAAIR of BT among persons who were non-Hispanic White and non-Hispanic American Indian/Alaska Native, while persons who were non-Hispanic Black, non-Hispanic Asian or Pacific Islander, and Hispanics had higher AAAIR in high pollution counties.

Conclusions: BT incidence overall and by behavior is increased in counties with high air pollution. Further studies are needed to support these findings in individual-level data, and to identify the mechanisms by which air pollution may affect BT risk.

A pharmacogenomic study of germline variants in DNA repair pathways and temozolomide toxicity in adults with glioma

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Background: The use of temozolomide (TMZ), along with maximum safe surgical resection and radiation is standard of care in the treatment of adults with high grade glioma (HGG). The benefit of TMZ in lower grade gliomas (LrGG) is complicated by a subset of patients that demonstrate somatic hypermutation at recurrence and shorter survival. Identifying risk for TMZ-mediated hypermutation has the potential to improve personalized medicine in gliomas and increase overall survival (OS). Prior work has largely focused on the role of MGMT promoter methylation, although DNA repair pathways, base excision repair (BER) and mismatch repair (MMR), are also mechanisms of action for TMZ. This pharmacogenomic SNP-drug interaction study aims to identify germline polymorphisms within genes located in the MMR and BER pathways which are associated with altered TMZ response in gliomas.

Materials and Methods: We utilized germline DNA of 1039 adults with glioma with TMZ exposure, and 443 cases without, recruited from the UCSF Adult Glioma Study (AGS) between 1998 and 2012. After pruning, our analysis included 2046 SNPs within 22 identified BER/MMR genes. We used OS time as a metric for drug effectiveness. Cox proportional hazards regression models for OS were used to detect significant SNP-TMZ interactions. SNP survival associations were then assessed using Kaplan Meier analyses separately for those with and without TMZ history to ensure the SNPs were drug specific. Analyses were conducted for *IDH* wildtype and mutant tumors separately.

Results: For *IDH* mutant gliomas, there was no significant difference in OS for TMZ exposed (n=215) versus not exposed (n=170), (*P*=0.53). SNPs within 4 genes (*MSH3*, *MSH2*, *MLH1*, *LIG4*) had significant (*P*<1e-5) interactive effects with TMZ on OS for cases with *IDH* mutant gliomas. Of particular interest, *IDH* mutant cases with the **rs1805389_A** polymorphism (A3V, MAF=0.054) in *LIG4* had significantly worse OS after TMZ exposure than those without the polymorphism (interaction term p-value =4.4e-84; two-year OS proportion 0.69 versus 0.92, respectively, *P*=0.013). Amongst *IDH* mutant cases without TMZ exposure, OS did not differ significantly by A3V polymorphism (two-year OS proportion 0.93 versus 0.92, *P*=0.86). Previous research has functionally identified A3V as impairing the catalytic function of the *LIG4* DNA repair gene, suggesting an alteration to the TMZ mechanism of action. These findings suggest a TMZ-specific SNP effect and potential risk factor for TMZ-induced hypermutation.
We did not detect significant (*P*<1e-5) SNP-TMZ interactions in *IDH* wildtype gliomas, although nominally significant associations are being further investigated.

Conclusions: This study aimed to identify if germline alterations in DNA repair pathways altered TMZ effectiveness in gliomas. Our most compelling association, the A3V polymorphism in *LIG4*, suggests those individuals harboring the mutation are at higher risk for shorter survival when treated with TMZ. We are actively validating these associations in an independent cohort and in a dataset of glioma cases with known TMZ-induced hypermutation. This work could provide improvements in the personalized usage of TMZ of adults with glioma.

Antibody Reactivity to Varicella Zoster Virus Improves Glioma Survival and is Modified by Germline HLA Polymorphisms

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Background:

Etiologic studies of glioma have shown inconsistent risk estimates associated with viral infections. Antigenic reactivity towards varicella zoster virus (VZV) has shown a consistent reduction in glioma risk across multiple studies on multiple continents. Using the UK BioBank we have previously shown that germline polymorphism, primary in the HLA, significantly effect reactivity to a variety of viral infections. In this study we investigate this association in the context of germline HLA polymorphisms known to influence reactivity to herpesviruses.

Materials and Methods:

We measured quantitative IgG reactivity towards VZV in 1378 adults with glioma. Associations of patient IgG levels with overall survival were estimated using Cox models adjusted for age, sex, self-reported race, surgery type, dexamethasone usage at blood draw, and tumor grade. Stratified analyses in 906 patients with whole genome array data were conducted based on a previously discovered HLA polymorphism that is associated with VZV antigen reactivity.

Results:

Overall, VZV antibody seropositivity was associated with improved survival outcomes in adults with glioma (HR = 0.70, 95% CI 0.54–0.90, *p*= .006). In the subset of patients with germline genetic data, the association remains (HR = 0.80 (0.68-0.94) p=0.0055). In patients with the VZV associated HLA polymorphism (n=257) no prognostic effect of VZV reactivity is observed (HR = 0.97 (0.70-1.34) p=0.847). In patients with the VZV associated HLA polymorphism (n=679) the survival benefit of high VZV reactivity is strengthened (HR = 0.73 (0.61-0.88) p=0.00097).

Conclusions:

A strong antibody response to VZV is associated with improved glioma prognosis. We observed evidence that the effect of VZV reactivity on glioma survival is modified by a specific HLA polymorphism. However, the complex linkage surrounding this polymorphism clouds SNP based analysis of this prognostic gene x virus association. Accounting for the HLA is critical for understanding the underlying mechanism. Investigating the effect of VZV vaccination on glioma risk and prognosis is warranted.

Exploring delays in diagnosis for children with brain and spinal cord tumors: A call to action.

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Background:

Childhood brain and spinal cord tumors are now the most common pediatric cancer, most common solid tumor, and the leading cause of disease-related mortality among children ages 0-19 years (CBTRUS, 2022) Delay in diagnosis is a term used widely to define the time interval from onset of symptoms to confirmed diagnosis (Mullen *et*. al, 2021). Our experience in caring for children with central nervous system (CNS) tumors has demonstrated a disconnect in perception of delay in diagnosis between caregivers and providers. Furthermore, there is no standardized data collection tool to assess delays in diagnosis, in order to explore its relationship with the patient journey, from diagnosis through long-term outcomes.

Timing of diagnosis of a brain or spinal cord tumor in a pediatric patient may be a predictor of clinical outcomes (Wilne *et*. al, 2013). The length of time from symptom onset to diagnosis may exacerbate caregiver distress which, in turn, impacts clinical outcomes. Associated social determinants of health (SDOHs), perceptions of credibility (*e.g.,* not being believed about symptoms), and negative interactions with health care providers may further exacerbate healthcare inequity.

Materials and Methods:

This study will develop metrics and survey items to quantify sources of delays in diagnosis to improve our understanding of causes and to promote greater timeliness in diagnoses. Caregiver interviews will allow us to assess the child's overall journey to diagnosis, including the child's symptom presentation, caregiver-provider communication attributes, and challenges to diagnosis. The pilot study will also capture data on SDOHs which are known to have a major impact on health and quality of life.

Consortium members in Colorado have developed a 30-minute workshop, based upon the success of the UK's HeadSmart campaign to increase awareness of pediatric CNS tumor symptoms among primary care practitioners and the general public, which has effectively led to a decrease in time to diagnosis. The educational tool has proved to be effective at increasing understanding of timely diagnosis of pediatric CNS tumors among Colorado's primary health care providers.

Results: The proposed work in being initiated at Indiana University and protocol approval is underway. The pilot study is expected to be conducted in May 2023.

Conclusions:

This proposed work will culminate in the creation of a validated assessment tool to standardize data collection on delays in diagnosis to be used prospectively by larger consortiums (e.g., Children's Oncology Group). This validated assessment tool could be incorporated into multilevel data systems, such as the NCI's Childhood Cancer Data Initiative, and contribute to the development of a comprehensive, national data repository. Integration of SDOHs data with genomics, radiomics, and other pertinent patient information will allow for a better understanding of long-term outcomes for patients with brain and spinal cord tumors. Using these data, we expected to develop actionable steps to reduce delays in diagnosis for brain and spinal cord tumors and, eventually, for all childhood cancers. These steps include changes in PCP training, new continuing education offerings from the American Academy of Pediatrics, and public health messaging to parents.

Genome-wide polygenic score for glioma improves risk prediction

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Background: Genome-wide association studies (GWAS) have identified over 20 risk loci for glioma. These findings have been used to generate polygenic risk scores (PRS), which quantify an individual's genetic susceptibility as a weighted sum of risk alleles. Previous PRS efforts have used a limited number of variants that reach genome-wide significance, which discards genetic information that could increase predictive accuracy. To develop a more powerful PRS for glioma we applied PRS-CS, an approach that uses continuous shrinkage priors to leverage genetic variation across the genome and account for linkage disequilibrium (LD).

Materials and Methods: Effects sizes for PRS-CS were inferred using European ancestry LD reference panels and GWAS meta-analysis summary statistics from the Glioma International Case Control Consortium for glioma overall (10,977 cases, 17,386 controls), glioblastoma (GBM; 5665 cases, 17,386 controls) and non-GBM (4,827 cases, 17,386 controls) tumors. The comparison PRS (PRSGSig) included 22 LD-independent variants with $p<5\times10\text{-}8$. The predictive performance of each score was evaluated in 867 cases (392 GBM, 477 non-GBM) from the Cancer Genome Atlas and 5,843 controls from the Wellcome Trust Case Control Consortium. Inverse probability weighting based on covariates and the top 10 genetic ancestry principal components was used to account for residual population structure due to the use of external controls.

Results: PRSCS was based on 1,077,444 variants present in HapMap3 and 1000 Genomes reference panels. For glioma overall PRSCS achieved higher classification accuracy (AUC=0.67, 95% CI: 0.65-0.70) with an odds ratio (OR) per standard deviation increase of 1.78 (95% CI: 1.62-1.95, $p=6.1\times10\text{-}34$) than PRSGSig (AUC=0.62, 0.60-0.64; OR=1.55, 1.43-1.67, $p=6.5\times10\text{-}29$). PRSCS trained on GBM GWAS summary statistics showed a modest improvement in prediction for GBM tumors (AUC=0.66; OR=1.73, $p=5.0\times10\text{-}15$) compared to PRSGsig (AUC=0.64; OR=1.65, $p=8.5\times10\text{-}16$). For non-GBM tumors, both approaches showed equivalent performance (AUC=0.68). To assess potential for bias due to partial control overlap (17%) between the GWAS training and validation data, we excluded overlapping samples from the GWAS meta-analysis and re-fit each PRS. The resulting scores were highly correlated ($0.91< r <0.99$), suggesting minimal impact on our results. Next, we evaluated the cross-phenotype portability of each PRS by testing it against molecular glioma subtypes based on *IDH* mutation and 1p19q co-deletion status. PRSCS developed using GWAS results for glioma overall showed a stronger association for *IDH*-wildtype tumors (OR=1.88, 1.62-2.19, $p=1.2\times10\text{-}16$; AUC=0.67) compared to PRSGsig (OR=1.43, $p=2.7\times10\text{-}9$; AUC=0.61). For *IDH*-mutated/1p19q co-deleted tumors, PRSCS trained using non-GBM GWAS data was more predictive (OR=3.02, $p=2.3\times10\text{-}9$; AUC=0.76) than PRSGsig (OR=2.07, $p=1.2\times10\text{-}7$; AUC=0.73). We also observed a larger magnitude of association for GBM PRSCS when applied to *IDH*-wildtype/1p19q non-deleted tumors (OR=1.76, 1.54-2.03, $p=8.9\times10\text{-}16$) compared to GBM PRSGSig (OR=1.62, 1.44-1.82, $p=3.5\times10\text{-}15$).

Conclusions: PRSCS achieved better discrimination for glioma and GBM tumors, suggesting that polygenic prediction methods that comprehensively model genetic architecture may be more powerful. Although we lacked GWAS data for molecular subtypes, PRSCS models were more predictive of *IDH*-wildtype tumors characterized by poor prognosis, even with suboptimal training data. Future directions for this work

include developing more refined PRSCS models to accurately characterize risk for molecular glioma subtypes.

Genomic and serologic evaluation of Alzheimer's disease risk factors in the etiology of glioblastoma

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Background: Glioblastoma (GBM) and Alzheimer's disease (AD) are two neurologic conditions with divergent epidemiologic risk factors. Of note, several GBM risk factors have been shown to protect against the development of AD, including male sex, non-Hispanic white race/ethnicity, longer telomere length, varicella sero-negativity, and higher educational attainment. To further evaluate etiologic heterogeneity between these two diseases, we explored genomic and serum biomarker profiles in patients with GBM, AD, and neurologically healthy controls.

Materials and Methods: We applied linkage disequilibrium score regression to genome-wide association study results of GBM risk (6183 GBM cases, 18169 controls) and AD risk 17008 AD cases, 37154 controls). We estimated genetic correlations between GBM and AD in European-ancestry populations using linkage disequilibrium score regression (LDSC), which leverages genome-wide single-nucleotide polymorphism (SNP) associations and patterns of linkage disequilibrium determined within the 1000 Genomes European reference population.

Results: The genomic architecture of these two diseases is not corelated at the genome-wide level (r_g=-1.27; P=0.06). Mendelian randomization analyses evaluating the effect of AD-associated SNPs (N=26) on risk of GBM showed a non-significant protective effect (-0.078, P_{IVW}=0.20). However, GBM-associated SNPs (N=16) significantly protected against risk of AD (-0.092, P_{IVW}<0.001). At the level of single SNPs, GBM-associated risk alleles that protect against AD risk are involved in diverse cellular pathways including receptor tyrosine kinase signaling, cell cycle control, and telomere maintenance. We also measured the ratio of β-amyloid 42/40, a validated biomarker of AD, in plasma from GBM patients, AD patients, and controls. As anticipated, AD patients had robustly lower Aβ 42/40 levels than controls. Interestingly, GBM patients had the highest Aβ 42/40 levels, significantly increased compared to even cognitively normal controls matched on age and sex ($P=4.8x10^{-4}$).

Conclusions: These results suggest that the etiology of GBM and AD are not just unique, but rather are directly opposed. Further research is needed to determine the extent to which this relationship may be modified by disparate pro- versus anti-inflammatory neural processes and neural/glial interactions

Region-based analyses of existing GWAS datasets discovers potential novel genetic risk regions for glioma

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Background: Glioma is a familial disease with a two-fold risk for individuals with an affected first-degree relative. Known genomic risk regions account for less than 40% of familial heritability[1]. Identification of new risk regions using conventional genome-wide association study (GWAS) is limited by the small sample sizes of glioma studies and stringent statistical thresholds. Our aim was to use machine learning tools that analyse genomic regions rather than individual genomic markers to explore glioma's missing heritability and potentially detect new glioma risk regions.

Methods: We undertook a genome-wide association analysis of three independent glioma case-control studies using two region-based approaches, a machine learning algorithm called DEPTH[2] and logistic regression with the Generalized Berk-Jones statistic (GBJ)[3]. Unlike conventional marginal analysis of GWAS data that consider each genomic marker independently, region-based methods analyse groups of genomic markers simultaneously. Both methods have been shown to discover risk regions missed by conventional GWAS analysis[3,4].

Results: We identified six potential novel glioma risk regions that showed strong replication in at least two of the three studies and in an aggregated analysis of the three studies combined. Five of these regions were discovered in sex-specific datasets and four of the six regions contain genes that have previously been linked with glioma tumour progression, suppression, or other cancers.

Conclusions: Our findings indicate that a region-based approach to GWAS may uncover some of glioma's missing heritability and that sex may affect a person's genetic susceptibility to glioma. Further research is necessary to identify the causal genetic variant(s) within these potential glioma risk regions.

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Title: Glioblastoma in the Real-World Setting: Patterns of Care and Outcome in the Austrian population

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Background:
The Austrian Brain Tumor Registry (ABTR) was implemented as a nationwide database for malignant and non-malignant brain tumors in the Austrian population (approx. 9 million inhabitants). Specific focus on glioblastoma including assessment of patterns of care and outcomes was set in a joint effort by the ABTR and the Society of Austrian Neurooncology (SANO), resulting in the ABTR-SANOnet database. Results extracted from the patient cohort with first surgery between 2014 and 2018 are presented.

Materials and Methods:
Patients newly diagnosed with glioblastoma between 01.01.2014 and 31.12.2018 all over Austria were included. Histological diagnosis used criteria of the World Health Organization (WHO) classification of tumors of the central nervous system, 4th updated edition 2016. Patterns of care were comprehensively assessed, and all patients were followed-up until 31.12.2019. This ABTR-SANOnet dataset was statistically analyzed.

Results:
1420 glioblastoma cases met inclusion criteria. 813 (57.3 %) patients are male and 607 (42.7 %) female, the M/F-ratio is 1.3. Median age at diagnosis is 64 years (ranging 18-88), and median overall survival is 11.6 months. A fraction of 225 (15.8 %) patients experienced prolonged survival (> 2 years), including elderly patients with incomplete tumor resection. Brain tumor surgery is frequently assisted by 5-ALA fluorescence. Postsurgical therapy regimens are very heterogenous, including use of therapy protocols for the elderly in some young patients, and full standard combined radiochemotherapy and adjuvant protocols in some elderly patients. Off-label use of anti-angiogenic therapy build an important element of patient care after first-line therapy. Tumor treating fields (TTFields) therapy is applied in < 5 % of patients, and statistically associates with favorable outcome.

Conclusions:
Our data illustrate an enormous heterogeneity of glioblastoma patient care in the real-world setting, including frequent off-label use of anti-angiogenic therapy in the recurrent disease setting. Overall median survival in our unselected glioblastoma patient cohort is lower than that reported in selected patient cohorts in controlled therapy trials. A small fraction of patients with an unfavorable prognostic profile (e.g., higher age and incomplete tumor resection) may still experience prolonged survival.

Associations between PM2.5, vegetation density and childhood brain tumors: a case-control registry-based study from Texas 1995-2011

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Background: Air pollution has been reported to be associated with some childhood cancers, namely leukemias. Less is known about air pollution and childhood brain tumor risk. In adult cancers, increasing vegetation density, or greenness, has been inversely associated with cancer incidence and survival. The interplay between air pollution and greenness, which co-occur, in childhood cancer etiology is unclear. Therefore, we sought to estimate the association between prenatal and early life exposure to air pollution, greenness, and childhood cancer in Texas (1995-2011).

Materials and Methods: We included 1,316 individuals with a childhood brain tumor diagnosed ≤16 years of age and 109,762 age- and sex-matched controls. We linked birth certificate residential address to census tract annual average particulate matter 2.5 μg/m³ (PM2.5) and Normalized Difference Vegetation Index (NDVI) to approximate prenatal and early life exposure to greenness and air pollution. We estimated odds ratios (OR) and 95% confidence intervals (95% CI) as the measure of association between PM2.5 and NDVI interquartile range (IQR) increases and brain tumors. Models were adjusted for birth year, sex, maternal race/ethnicity, and arealevel socioeconomic status (Yost index).

Results: The following brain tumor types were included: ependymoma (n=136), astrocytoma (n=619), medulloblastoma (n=187), PNET (n=57), ATRT (n=54), and other gliomas (n=263). Average birth year PM2.5 and NDVI exposure levels were similar in cases and controls, 11 μg/m³ and 0.4, respectively. Each IQR increase (2.6 μg/m³) in PM2.5 was associated with ependymoma (OR: 1.27, 95% CI: 1.01-1.60) when adjusting for control-derived quartiles of NDVI. Conversely, after adjusting for PM2.5 quartiles, each IQR increase in NDVI (0.13) was inversely associated with ependymoma in those diagnosed at 0-4 years of age (OR: 0.75, 95% CI: 0.56-0.97) and with medulloblastoma in those aged 0-16 years at diagnosis (OR: 0.75, 95% CI: 0.62-0.91). There was no evidence of statistical interaction between NDVI and PM2.5 (all Likelihood Ratio Test p values> 0.05) for any brain tumors.

Conclusions: Increasing residential air pollution during prenatal and early life increased the risk of childhood ependymoma in Texas independent of greenness. Conversely, increasing greenness exposure in prenatal and early life decreased the risk of ependymoma and medulloblastoma independent of PM2.5.

These findings highlight the complex relationship between air pollution and greenness in childhood cancer etiology.