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### CBTRUS Statistical Report: Pediatric Brain Tumor Foundation Childhood and Adolescent Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2014–2018

### Quinn T. Ostrom, Mackenzie Price, Katherine Ryan, Jacob Edelson, Corey Neff, Gino Cioffi, Kristin A. Waite, Carol Kruchko, and Jill S. Barnholtz-Sloan

Central Brain Tumor Registry of the United States, Hinsdale, Illinois, USA (Q.T.O., M.P., C.N., G.C., K.A.W., C.K.,J.S.B.-S.); Department of Neurosurgery, Duke University School of Medicine, Durham, North Carolina, USA (Q.T.O., M.P., K.R., C.N.); The Preston Robert Tisch Brain Tumor Center, Duke University School of Medicine, Durham, North Carolina, USA (Q.T.O., K.R.); Duke Cancer Institute, Duke University School of Medicine, Durham, North Carolina, USA (Q.T.O.); Trans Divisional Research Program (TDRP), Division of Cancer Epidemiology and Genetics (DCEG), National Cancer Institute, Bethesda, Maryland, USA (J.E., G.C., K.A.W., J.S.B.-S.); Center for Biomedical Informatics & Information Technology (CBIIT), National Cancer Institute, Bethesda, USA (J.S.B.-S.)

Corresponding Author: Quinn T. Ostrom, Ph.D., M.P.H., Duke University School of Medicine, DUMC Box 3050, Durham, NC 27710, Email: Quinn.Ostrom@duke.edu

#### Abstract

The CBTRUS Statistical Report: Pediatric Brain Tumor Foundation Childhood and Adolescent Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2014–2018 comprehensively describes the current population-based incidence of primary malignant and non-malignant brain and other CNS tumors in children and adolescents ages 0–19 years, collected and reported by central cancer registries covering approximately 100% of the United States population. Overall, brain and other CNS tumors are the most common solid tumor, the most common cancer, and the most common cause of cancer death in children and adolescents ages 0–19 years. This report aims to serve as a useful resource for researchers, clinicians, patients, and families.

### **Executive Summary**

The Central Brain Tumor Registry of the United States (CBTRUS), in collaboration with the Centers for Disease Control and Prevention (CDC) and National Cancer Institute (NCI), is the largest population-based registry focused exclusively on primary brain and other central nervous system (CNS) tumors in the United States and represents the entire United States population. The *CBTRUS Statistical Report: Pediatric Brain Tumor Foundation Childhood and Adolescent Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2014–2018* contains the most up-to-date population-based data on primary brain and other CNS tumors in children and adolescents available through

the surveillance system in the United States and supersedes all previous reports in terms of completeness and accuracy, thereby providing a current comprehensive source for the descriptive epidemiology of these tumors.

### Incidence

 The annual average age-specific incidence rate of all malignant and non-malignant brain and other CNS tumors in children and adolescents ages 0–19 years was 6.23 per 100,000 population between 2014 and 2018. When stratified by behavior, incidence was 3.55 per 100,000 population for malignant tumors only, and 2.67 for non-malignant tumors only.

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- This overall rate was higher in females compared to males (6.35 versus 6.11 per 100,000) and non-Hispanics (of any race) compared to Hispanics (6.52 versus 5.33 per 100,000).
- An estimated 5,260 new cases of malignant and nonmalignant brain and other CNS tumors are expected to be diagnosed in children and adolescents ages 0–19 years in the United States in 2023.

#### Mortality

 There were 2,693 deaths attributed to malignant brain and other CNS tumors between 2014 and 2018 in children and adolescents ages 0–19 years. This represents an annual average mortality rate of 0.66 per 100,000 population, and an average of 539 deaths per year caused by malignant brain and other CNS tumors.

#### Survival

 The five-year relative survival rate following diagnosis of a malignant or non-malignant brain or other CNS tumor was 83.9%. Survival following diagnosis with a brain and other CNS tumor was highest in adolescents ages 15–19 years (90.5%) and lowest in children less than one year old (71.9%).

#### Prevalence

- There were an estimated 40,594 children and adolescents ages 0–19 years living with a primary brain and other CNS tumor diagnosis in 2022. This is comparable to leukemia, where there are an estimated 40,738 children and adolescents ages 0–19 years living with a leukemia diagnosis.
- The most prevalent histopathologic group was pilocytic astrocytoma (estimated 8,264 cases).

### Introduction

Brain tumors are a significant source of cancer-related morbidity and mortality in children and adolescents. This age group is diagnosed with unique groups of cancers and requires separate reporting in order to accurately portray the state of brain tumors in these populations.

The Central Brain Tumor Registry of the United States (CBTRUS) is the largest population-based registry of primary brain and other central nervous system (CNS) tumors in the United States and covers ~100% of the United States (US) population for the period between 2014 and 2018. The objective of the *CBTRUS Statistical Report: Pediatric Brain Tumor Foundation Childhood and Adolescent Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2014–2018* is to provide a comprehensive summary of the current descriptive epidemiology of primary brain and other CNS tumors of childhood and adolescence (ages 0–19 years) in the US population. CBTRUS obtained all newly diagnosed primary brain and other CNS tumors data submitted to the Centers for Disease Control and Prevention's (CDC) National Program of Cancer Registries (NPCR) and the National Cancer Institute's (NCI) Surveillance, Epidemiology and Results (SEER) Program in November 2020 and covered diagnosis years 2000–2018. Incidence counts and rates of primary brain and other CNS tumors are documented by histopathology, sex, age, race, and Hispanic ethnicity. Mortality and relative survival rates calculated using NPCR data for the period 2001–2017 are also presented.

### Background

CBTRUS is currently the only population-based sitespecific registry in the United States that works in partnership with a public cancer surveillance organization, the CDC's NPCR, and from which data are directly received under a special agreement. This agreement permits transfer of data through the National Program of Central Registries Cancer Surveillance System (NPCR-CSS) Submission Specifications mechanism. CBTRUS researchers combine the NPCR data with data from the SEER Program<sup>1</sup> of the NCI, which was established for national cancer surveillance in the early 1970s. All data from NPCR and SEER originate from tumor registrars who adhere to the Uniform Data Standards (UDS) for malignant and nonmalignant brain and other CNS tumors as directed by the North American Association of Central Cancer Registries (NAACCR) (http://www.naaccr.org). Along with the UDS, there are guality control checks and a system for rating each central cancer registry (CCR) to further ensure that these data are reported as accurately and completely as possible. As a surveillance partner, CBTRUS can therefore report high quality data on brain and CNS tumors with histopathological specificity useful to the communities it serves. Its database represents the largest aggregation of population-based data on the incidence of primary brain and other CNS tumors in the United States.

### **Technical Notes**

### Data Collection

CBTRUS contains incidence data from 52 independent CCRs (48 NPCR and 4 SEER registries) representing ~98% of the US population for the time period examined in this report. Please see the 2021 CBTRUS Statistical Report for additional information about the way these data are obtained and processed. These cases are classified using the International Classification of Diseases for Oncology, Third edition (ICD-O-3) for assignment of histopathology, behavior, and site codes. These codes are grouped using a modified version of the CBTRUS Grouping (Supplementary Table 1).<sup>2</sup> As there is no standard definition for glioma, **CBTRUS defines glioma as ICD-O-3 histopathology codes 9380–9384, and 9391–9460**. It is also important to note that the statistics for lymphomas and hematopoietic neoplasms contained in this report refer only to those lymphomas and hematopoietic neoplasms that arise in the brain and other CNS ICD-O-3 topography codes.

Primary brain and other CNS tumors can be broadly classified in non-malignant (ICD-O-3 behavior codes of /0 for benign and /1 for uncertain) and malignant (ICD-O-3 behavior code of /3). Collection of central (state) cancer data was mandated in 1992 by Public Law 102–515 for all primary malignant tumors (ICD-O-3 behavior code of /3) (Supplementary Table 1), the Cancer Registries Amendment Act.<sup>3</sup> This mandate was expanded to include **non-malignant brain and other CNS tumors** (ICD-O-3 behavior code of /0 and /1) with the 2002 passage of Public Law 107–260, starting January 1, 2004.<sup>4</sup> See Supplementary Table 3 for a summary of specific glioma histopathologies included in glioma groupings.

Pilocytic astrocytoma is clinically considered and classified as a Grade I, non-malignant (ICD-O-3 behavior code of /1) tumor by the World Health Organization (WHO) guidelines for brain and other CNS tumors.<sup>5</sup> For the purposes of cancer registration, these tumors have historically been reported as malignant (ICD-O-3 behavior code of /3) tumors both in the United States and by the International Agency for Research on Cancer (IARC) and International Association of Cancer Registries.<sup>6,7</sup> Classification of these tumors as malignant has been followed by CBTRUS in its reporting unless otherwise stated. Classification of these tumors as malignant has a significant impact on both incidence and survival estimates (Figure 1), including an upward bias for both incidence of malignant tumors and survival estimates for malignant brain tumors. Please see a recent publication for additional discussion of the effect of this classification on cancer incidence and survival reporting.8

Age-specific incidence rates per 100,000 population for the entire United States for selected other cancers were obtained from the United States Cancer Statistics (USCS), produced by CDC and NCI, for the purpose of comparison with brain and other CNS tumor incidence rates.<sup>9</sup> This database includes both NPCR and SEER data and represents the entire US population. Comparison cancers are classified using the International Classification of Childhood Cancer (ICCC) grouping system. ICCC categories for this report were generated using the SEER *Main and Extended Classification for ICCC Recode ICD-O-3/WHO 2008*<sup>10</sup> based on the ICCC, Third edition<sup>11,12</sup> and *2007 WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*<sup>13</sup>

De-identified survival data for malignant brain and other CNS tumors were obtained from the USCS program for 42 NPCR registries with available survival data for the years 2001 to 2017 and for non-malignant brain and other CNS tumors for the years 2004 to 2017 (data collection for nonmalignant tumors began in 2004). This dataset provides population-based information for 82% of the US population for the years 2001 to 2017 and is a subset of the data used for the incidence calculations presented in this report. Survival information is derived from both active and passive follow-up.

Mortality data for the years 2014 to 2018 used in this report are from the National Vital Statistics System (NVSS) and include deaths where primary brain or other CNS tumor was listed as primary cause of death on the death certificate for individuals from all 50 states and the District of Columbia. These NVSS<sup>14</sup> (includes death certification data for 100% of the US population) data were obtained from the NCI via SEER\*Stat malignant brain and other CNS tumors and comparison (for malignant brain tumors and



Abbreviations: CBTRUS, Central Brain Tumor Registry of the United States; NPCR, National Program of Cancer Registries; SEER, Surveillance, Epidemiology and End Results Program; w/, with; w/o, without; PA, pilocytic astrocytoma.

Fig. 1 Effect of Reclassification of Pilocytic Astrocytoma from Malignant to Non-Malignant Behavior for Diagnoses in Children and Adolescents Ages 0–19 Years on A) Average Annual Incidence from 2014–2018 and B) Relative Survival after Diagnosis from 2004–2017, CBTRUS Childhood and Adolescent Report: US Cancer Statistics—NPCR and SEER, 2014–2018.

comparison cancers). NVSS data are not collected through the cancer registration system. These data represent the primary cause of death listed on each individual death certificate, and as a result, deaths in persons with cancer may be recorded as non-cancer deaths.

#### Methods

Counts, means, medians, rates, ratios, proportions, and other relevant statistics were calculated using R 4.1.3 statistical software<sup>15</sup> and/or SEER\*Stat 8.4.0.<sup>16</sup> Figures and tables were created in R 4.1.3 using the following packages: flextable, officer, orca, plotly, SEER2R, sf, tigris, and tidyverse.<sup>17-25</sup> Rates are suppressed when counts are fewer than 16 within a cell but included in totals, except when data are suppressed from only one cell to prevent identification of the number in the suppressed cell. **NOTE: reported percentages may not add up to 100% due to rounding.** 

Incidence and Mortality Rates.- Age-specific incidence and mortality rates and 95% confidence intervals<sup>26</sup> (CI) were estimated for malignant and non-malignant tumors and for selected histopathology groupings by sex, race, Hispanic ethnicity, and age groups. Estimates are presented by age groups < 1, 1-4, 5-9, 10-14, and 15-19 years. Race categories in this report are all races, White, Black, American Indian/Alaskan Native (AIAN), and Asian/Pacific Islander (API). Other race, unspecified, and unknown race are included in statistics that are not racespecific. Hispanic ethnicity was defined using the NAACCR Hispanic Identification Algorithm, version 2, data element, which utilizes a combination of cancer registry data fields (Spanish/Hispanic Origin data element, birthplace, race, and surnames) to directly and indirectly classify cases as Hispanic or non-Hispanic.<sup>27</sup> The NAACCR regional scheme (http://faststats.naaccr.org/usregions.php) was used for statistics reported by region of the United States.

Incidence rate ratios (IRR) were generated based on these age-specific incidence rates. These IRR were used to compare groups, using the formulas described by Fay et al. to calculate p-values.<sup>28</sup> IRR were considered statistically significantly different when the p-value was less than 0.05.

*Estimated Future Cases.*— Estimated numbers of expected malignant and non-malignant brain and other CNS tumors were calculated for 2023–2025. To project estimates of newly diagnosed brain and other CNS tumors, age-specific annual brain tumor incidence rates were generated for 2000–2018 for malignant tumors, and 2006–2018 (years 2004–2005 excluded as these were the first few years of data collection during which incidence increased significantly) for non-malignant tumors. These were generated by state, age, and histopathologic type. Joinpoint 4.9.0.0<sup>29</sup> was used to fit regression models to these incidence rates,<sup>30</sup> which were used to predict numbers of cases in future years using the parameter from the selected models. Modified Bayesian Information Criterion procedures included in Joinpoint were used to select the

best fitting model. The overall totals presented are based on total malignant and non-malignant incidence, and the presented stratified rates may not add up to these totals. Estimated numbers of cases are highly dependent on input data. Different patterns of incidence within strata can significantly affect the projected estimates, especially when the number of cases within a stratum is low. Estimates are generated with the assumption of consistent trends in cases and population. **Caution should be used when utilizing these estimates**.

*Estimation of Relative Survival.*— SEER\*Stat 8.4.0 statistical software was used to estimate one-, two-, three-, four-, five-, and ten-year relative survival rates for primary **malignant** and **non-malignant** brain and other CNS tumor cases diagnosed between 2004–2017 in 42 NPCR CCRs. This software utilizes life-table (actuarial) methods to compute survival estimates and accounts for current follow-up. Second or later primary tumors, cases diagnosed at autopsy, cases in which race or sex is coded as other or unknown, and cases known to be alive but for whom follow-up time could not be calculated, were excluded from survival data analyses prior to release of the survival dataset to CBTRUS by NPCR.

**Prevalence** Estimation.— For estimation of brain and other CNS tumor prevalence, new case count data by histopathology and single age at diagnosis for malignant and non-malignant brain tumors (2004–2018 for non-malignant tumors) were extracted from CBTRUS from 2000–2018 and from SEER 9 for 1975–2018. For comparison cancers, new case count data by ICCCdefined histopathology and single age at diagnosis from USCS for 2001–2018 and from SEER 9 for 1975– 2018. New case diagnoses and survival were projected from 2019–2022 using *prevEst* in R 4.0, which were then used to estimate total number of prevalent cases by histopathology and age for the year at prevalence, 2022.

Incidence and Mortality Trends.- Joinpoint 4.9.0.029 was used to estimate incidence and mortality time trends and generate annual percentage changes (APC) and 95% Cl. Rather than calculating a single consistent slope of change over an entire period of time, Joinpoint allows for points where the slope of the trend can change during the time period (joinpoints). This method starts with a model that assumes one consistent trend over time, and tests whether the addition of these "joinpoints" result in a model which has a fit that represents a statistically significant improvement over the model with no joinpoints. These models are tested through use of Monte Carlo permutations, e.g., the program repeats the same analysis multiple times using random samples to identify the "true" proportion of times that a comparison is statistically significant. The models allowed for a maximum of three joinpoints (two for non-malignant tumors), a minimum of three years from a joinpoint to either end of the time-period, and a minimum of three years between joinpoints.31

Survival Trends. - For analysis of survival trends, year of diagnosis was divided into 3, equal time periods: 2004-2007, 2008-2012, and 2013-2017. Univariate Kaplan-Meier analysis was performed to assess differences in overall survival by time-period in individuals 0-19 years of age. Kaplan-Meier survival curves were generated for patients with a high-grade glioma and then specifically for patients with a medulloblastoma. Log rank tests were performed to evaluate differences in survival curves. Age-stratified multivariable Cox proportional hazard models, adjusted for sex, race/ethnicity, and treatment, were performed for each time-period, hazard ratios (HR) and associated 95% CI are reported. Surgery subgroups were defined by SEER site specific surgery codes for primary brain and CNS: no surgery (00), excisional/subtotal resection (20, 21, 40), and gross total resection (30, 55). Treatment was defined on the basis of radiation and surgery received. The Cox proportional hazard assumptions were tested and models were not found to be in violation.

### **Results**

Overall, the annual average age-specific incidence rate of all malignant and non-malignant brain and other CNS tumors in children and adolescents ages 0–19 years was 6.23 per 100,000 population between 2014 and 2018, for an average of 5,099 newly diagnosed cases per year (Figure 2). During the same period, there were 2,693 deaths attributed to malignant brain and other CNS tumors in children and adolescents ages 0–19 years. This represents an annual average mortality rate of 0.66 per 100,000 population, and an average of 539 deaths per year caused by malignant brain and other CNS tumors (Figure 2).



Fig. 2 Annual Incidence Rates of All Primary Brain and Other Central Nervous System Tumors and Mortality Rates of Malignant Primary Brain and Other Central Nervous System Tumors in Children and Adolescents Ages 0–19 Years, CBTRUS Childhood and Adolescent Report: US Cancer Statistics—NPCR and SEER, 2004–2018.

### Central Cancer (State) Registry-Specific and Regional Brain Tumor Incidence Rates

The overall incidence rates for all primary brain and other central nervous system tumors and glioma in children and adolescents by CCR are shown in Figure 3 and Supplementary Table 4.

- Incidence of brain and other CNS tumors (Figure 3A), and glioma (Figure 3B) varied by CCR. Regional variations between CCR likely reflect differences in reporting and case ascertainment practices, as well as demographic differences in the underlying population that are associated with variation in brain and CNS tumor risk.
- There is slight variation by region for all brain and other CNS tumor incidence rates by age group. Please see Supplementary Figure 1 for incidence of children and adolescents ages 0–4, 5–9, 10–14, and 15–19 years.
- Internationally, incidence (Supplementary Figure 2A) and mortality (Supplementary Figure 2B) due to primary brain and other CNS tumors in children and adolescents 0–19 years of age varied by country and region.
- Higher income countries have higher average annual incidence than their counterparts, with the United States and Canada representing regions with the highest incidence of childhood and adolescent brain and other CNS tumors.

### Frequency of Brain and Other CNS Tumor Histopathologies

The distribution of brain and other CNS tumors in children and adolescents ages 0–19 years by site is shown in Figure 4A.

- The most common site was the pituitary and craniopharyngeal duct (17.7%), followed by the cerebellum (14.3%).
- While tumors in the brain stem accounted for 10% of all tumors, it is the primary site (~60%) for high grade glioma tumors (Figure 4B).
- Cerebrum, ventricle, and brain stem accounted for 5.4%, 5.2%, and 10%.
- Other brain is a designation used in cancer registry data when the location of a tumor is not identified in a patient's record, or when a tumor involves multiple locations in the brain. Please refer to Supplementary Table 1 for more information about the specific sites included in these groups.

The distribution of childhood and adolescent brain and other CNS tumors by histopathology is shown in Figure 4B. Frequencies for each histopathology are presented in Table 2. Frequencies by age groups are presented in Supplementary Figures 3–7.

- The most frequently reported histopathology in all ages (0–19 years) was pilocytic astrocytoma (15.3%).
- Tumors of the pituitary accounted for 14.3% of all childhood and adolescent brain and other CNS tumor histopathologies.



Fig. 3 Average Annual Age-Specific Incidence Rates per 100,000 Population of A) All Primary Malignant and Non-Malignant Brain and Other Central Nervous System Tumors, and B) Glioma in Children and Adolescents Ages 0–19 Years by Central Cancer Registry, CBTRUS Childhood and Adolescent Report: US Cancer Statistics—NPCR and SEER, 2014–2018.

- In infants (<1 year of age), gliomas (32.0%) and embryonal tumors (20.8%) were the most commonly occurring tumor type. Of embryonal tumors, 55.6% were atypical teratoid/rhabdoid tumors (ATRT).
- In children ages 1–4 years and 5–9 years, gliomas (50.5% and 50.3%, respectively) and embryonal tumors (16.7% and 13.1%, respectively) were the most common tumor types. Among children 1–4 years, 58% of embryonal tumors were medulloblastomas.







**Fig. 4** Distribution<sup>a</sup> in Children and Adolescents Ages 0–19 Years of All Primary Malignant and Non-Malignant Brain and Other Central Nervous System Tumors (Five-Year Total = 25,497; Annual Average Cases = 5,099) by A) Site and B) Histopathology, CBTRUS Childhood and Adolescent Report: US Cancer Statistics—NPCR and SEER, 2014–2018.

- In children ages 10–14 years, gliomas (43.0%) and tumors of the pituitary (12.3%) were the most common tumor types.
- In adolescents ages 15–19 years, tumors of the pituitary (33.0%) were the most common tumor type, followed by gliomas (27.7%).

### Age-Specific Incidence Rates

Incidence Rates by Age at Diagnosis.— The overall age-specific incidence rate for 2014–2018 for all primary brain and other CNS tumors in children and adolescents (0–19 years of age) was 6.23 per 100,000 population (Table 1). The overall incidence rate was 6.31 per 100,000 population for children 4 year of age, 6.12 per 100,000 population for children ages 1–4 years, 5.53 per 100,000 population for children ages 5–9 years, 5.88 per 100,000 population for adolescents ages 10–14 years, and 7.31 per 100,000 population for adolescents ages 15–19 years.

Incidence Rates by Age at Diagnosis and Histopathology— The age-specific incidence rates by age and histopathology at diagnosis are shown in Table 3.

 Overall incidence rates of all brain and other CNS tumors by histopathology declined with increasing age from < 1 year of age to 10–14 years groups. Adolescents ages 15–19 years had the highest annual average agespecific incidence rate for all primary brain and other CNS tumors (7.31 per 100,000).

- The incidence rates of all gliomas were highest in children ages 1–4 years (3.55 per 100,000) and lowest among adolescents ages 15–19 years (2.23 per 100,000).
- Incidence rates of choroid plexus tumors, embryonal tumors, choroid plexus tumors decreased with age, respectively.
- Incidence rates of neuronal and mixed neuronal-glial tumors, tumors of the cranial and spinal nerves, and tumors of the sellar region increased with age.

Diffuse intrinsic pontine glioma (DIPG) is a particularly devastating type of high-grade glioma that occurs in children. These tumors do not have a distinct ICD-O-3 site code in cancer registry data, but incidence of high-grade glioma of the brain stem is presented in Table 4.

- Overall incidence rate of high-grade glioma of the brain stem was 0.35 per 100,000 population.
- These tumors occurred more frequently in children ages 5–9 years, where incidence is 0.56 per 100,000 population.
- Incidence of these tumors was highest in White (0.34 per 100,000) and Black (0.38 per 100,000) children and adolescents, and was higher in non-Hispanic (0.37 per 100,000) as compared to Hispanic (0.28 per 100,000) children and adolescents.

Age-Specific Incidence Rates by Site and Age Groups— Incidence rates for each site by age are shown in Table 5.

• The site with the highest incidence of brain and other CNS tumors was the pituitary gland (0.95 per 100,000), followed by cerebellum (0.89 per 100,000).

Group	Incidence R	ate (2014–2018)					Mortality	r Rate (2014–2018)	5-year Relative Su	urvival (2001–201	(2)
	Total		Malignan	t <sup>c</sup>	Non-Mali	gnant <sup>d</sup>	Malignar	nt Only≏	Total	<b>Aalignant<sup>°</sup></b>	Non-Malignant <sup>a</sup>
	Annual Average Cases	Rate (95% CI)	Annual Average Cases	Rate (95% CI)	Annual Average Cases	Rate (95% CI)	Annual Average Deaths	Rate (95% CI)	RS (95%CI) (9	IS 95% CI)	RS (95% CI)
Sex											
Male	2,556	6.11 (6.00–6.22)	1,584	3.78 (3.70–3.87)	972	2.32 (2.26–2.39)	297	0.71 (0.67-0.75)	82.8 (82.3–83.2) 7	5.7 (75.1–76.3)	97.7 (97.4–98.1)
Female	2,543	6.35 (6.24–6.46)	1,326	3.31 (3.23–3.39)	1,217	3.04 (2.96–3.12)	242	0.60 (0.57-0.64)	85.1 (84.7–85.5) 7	5.6 (74.9–76.2)	98.4 (98.1–98.6)
Age Group											
<1 year	247	6.31 (5.96–6.67)	152	3.89 (3.62–4.18)	95	2.42 (2.21–2.65)	12	0.31 (0.24-0.40)	71.9 (70.3–73.4) 6	0.3 (58.1–62.3)	94.1 (92.5–95.4)
1–4 years	974	6.12 (5.95–6.29)	744	4.67 (4.52–4.83)	230	1.44 (1.36–1.53)	85	0.54 (0.49–0.59)	79.3 (78.5–80.0) 7.	4.6 (73.7–75.4)	97.4 (96.7–98.0)
5-9 years	1,126	5.53 (5.39–5.68)	779	3.83 (3.71–3.95)	347	1.71 (1.63–1.79)	190	0.93 (0.87-0.99)	79.9 (79.2–80.6) 7	3.6 (72.7–74.5)	97.6 (97.0–98.1)
10–14 years	1,215	5.88 (5.73-6.03)	685	3.31 (3.20–3.43)	530	2.56 (2.47–2.66)	138	0.67 (0.62-0.72)	87.0 (86.4–87.6) 8	0.1 (79.3–81.0)	98.2 (97.8–98.6)
15-19 years	1,538	7.31 (7.14–7.47)	550	2.61 (2.51–2.71)	988	4.69 (4.56–4.83)	114	0.54 (0.50-0.58)	90.5 (90.0–90.9) 7	9.3 (78.3–80.2)	98.9 (98.6–99.1)
Race											
White	3,971	6.44 (6.35–6.53)	2,276	3.69 (3.62–3.76)	1,695	2.75 (2.69–2.81)	415	0.68 (0.65-0.70)	84.6 (84.3–84.9) 7	6.8 (76.3–77.3)	98.2 (98.0–98.4)
Black	665	4.88 (4.71–5.05)	373	2.73 (2.61–2.86)	293	2.15 (2.04–2.26)	88	0.65 (0.59-0.71)	79.1 (78.1–80.0) 6	8.3 (66.9–69.6)	96.9 (96.1–97.5)
American Indian/ Alaska Native	51	3.31 (2.92–3.75)	27	1.79 (1.51–2.12)	23	1.52 (1.26–1.82)	٢	0.45 (0.31–0.63)	83.7 (80.4–86.5) 7	1.7 (66.5–76.2)	99.8 (92.0–100.0)
Asian or Pacific Islander	288	5.66 (5.37–5.96)	166	3.26 (3.04–3.49)	122	2.40 (2.21–2.60)	28	0.55 (0.47–0.65)	80.6 (78.9–82.2) 7	1.3 (68.9–73.6)	98.1 (96.9–98.9)
Ethnicity											
Non-Hispanic	4,026	6.52 (6.43–6.61)	2,347	3.80 (3.73–3.87)	1,679	2.72 (2.66–2.78)	416	0.68 (0.65-0.71)	84.4 (84.0-84.7) 7	6.5 (76.1–77.0)	98.2 (98.0–98.4)
Hispanic	1,073	5.33 (5.19–5.47)	563	2.79 (2.69–2.90)	510	2.53 (2.44–2.63)	122	0.60 (0.55-0.65)	82.1 (81.4–82.8) 7	1.7 (70.6–72.7)	97.8 (97.3–98.2)
Total	5,099	6.23 (6.15–6.30)	2,910	3.55 (3.50–3.61)	2,190	2.67 (2.62–2.72)	539	0.66 (0.63–0.68)	83.9 (83.6–84.2) 7	5.6 (75.2–76.1)	98.1 (97.9–98.3)
<sup>a</sup> Annual average case <sup>b</sup> Rates are per 100,000 <sup>c</sup> Assigned behavior co <sup>d</sup> Assigned behavior co	s are calculat ). ode of/3 by the ode of/0 or/1 by	ed by dividing the fiv International Classified the International Cl	e-year total "ication for l assification	l by five. Disease, Oncology 3 <sup>rc</sup> for Disease, Oncolog	<sup>d</sup> edition (ser 3y 3 <sup>rd</sup> editior	e Supplementary Tak 1 (see Supplementar	ole 3). y Table 3).	- - - - -	- - - -	: : :	-
Abbreviations: CB1	RUS, Central I	Brain Tumor Registry	of the Unite	ed States; Cl, confide	nce interval	; NPCR, National Prc	ogram of Ca	ancer Registries; RS	S, Relative Survival; S	EER, Surveillance,	Epiden

Table 1. Average Cases<sup>6</sup>, Age-Specific Incidence Rates<sup>b</sup>, Average Amnual Deaths, Age-Specific Mortality Rates<sup>b</sup>, and Five-Year Relative Survival with 95% Confidence Intervals for Brain and Other Central

End Results Program; NCI, National Cancer Institute; CDC, Centers for Disease Control and Prevention; NCHS, National Center for Health Statistics; NVSS, National Vital Statistics System.

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Histopathology	Total					Male			Female		
	Total Cases (2014–2018)	Annual Average	Median Age	% All tu- mors	Rate (95% Cl)	Total Cases (2014–2018)	Annual Average	Rate (95% CI)	Total Cases (2014–2018)	Annual Average	Rate (95% CI)
Gliomas <sup>b</sup>	11,474	2,295	80	45.0	2.80 (2.75–2.85)	6,041	1,208	2.89 (2.82–2.96)	5,433	1,087	2.71 (2.64–2.79)
Pilocytic astrocytoma	3,877	775	7	15.2	0.95 (0.92–0.98)	1,983	397	0.95 (0.91–0.99)	1,894	379	0.95 (0.90-0.99)
Other Low grade glioma	2,164	433	11	8.5	0.53 (0.51–0.55)	1,188	238	0.57 (0.54–0.60)	976	195	0.49 (0.46–0.52)
High grade glioma	2,361	472	6	9.3	0.58 (0.55–0.60)	1,214	243	0.58 (0.55–0.61)	1,147	229	0.57 (0.54–0.61)
Other glioma	6,949	1,390	7	27.3	1.70 (1.66–1.74)	3,639	728	1.74 (1.68–1.80)	3,310	662	1.65 (1.60–1.71)
Ependymal tumors	1,176	235	7	4.6	0.29 (0.27–0.30)	664	133	0.32 (0.29–0.34)	512	102	0.26 (0.23-0.28)
Choroid plexus tumors	416	83	2	1.6	0.10 (0.09–0.11)	238	48	0.11 (0.10–0.13)	178	36	0.09 (0.08–0.10)
Neuronal and mixed neuronal- glial tumors	1,282	256	12	5.0	0.31 (0.30–0.33)	697	139	0.33 (0.31–0.36)	585	117	0.29 (0.27–0.32)
Tumors of the pineal region	213	43	6	0.8	0.05 (0.05–0.06)	107	21	0.05 (0.04-0.06)	106	21	0.05 (0.04–0.06)
Embryonal tumors	2,397	479	2	9.4	0.59 (0.56–0.61)	1,431	286	0.68 (0.65–0.72)	996	193	0.48 (0.45–0.51)
Medulloblastoma	1,662	332	7	6.5	0.41 (0.39–0.43)	1,063	213	0.51 (0.48–0.54)	599	120	0.30 (0.28–0.32)
ATRT	383	77	1	1.5	0.09 (0.08–0.10)	191	38	0.09 (0.08–0.11)	192	38	0.10 (0.08–0.11)
Other embryonal tumors	352	70	e	1.4	0.09 (0.08–0.10)	177	35	0.08 (0.07–0.10)	175	35	0.09 (0.07–0.10)
Tumors of cranial and spinal nerves	1,202	240	12	4.7	0.29 (0.28–0.31)	651	130	0.31 (0.29–0.34)	551	110	0.28 (0.25–0.30)
Tumors of meninges	1,291	258	14	5.1	0.32 (0.30–0.33)	622	124	0.30 (0.27–0.32)	669	134	0.33 (0.31–0.36)
Lymphomas and hematopoietic neoplasms	135	27	11	0.5	0.03 (0.03–0.04)	78	16	0.04 (0.03–0.05)	57	11	0.03 (0.02–0.04)
Germ cell tumors	849	170	12	3.3	0.21 (0.19–0.22)	596	119	0.28 (0.26-0.31)	253	51	0.13 (0.11–0.14)
Tumors of sellar region	4,484	897	16	17.6	1.10 (1.06–1.13)	1,420	284	0.68 (0.64–0.72)	3,064	613	1.53 (1.48–1.58)
Tumors of the pituitary	3,639	728	16	14.3	0.89 (0.86–0.92)	946	189	0.45 (0.42–0.48)	2,693	539	1.34 (1.29–1.40)
Craniopharyngioma	845	169	6	3.3	0.21 (0.19–0.22)	474	95	0.23 (0.21–0.25)	371	74	0.19 (0.17–0.21)
UnclassifiedTumors	1,570	314	11	6.2	0.38 (0.36–0.40)	808	162	0.39 (0.36–0.41)	762	152	0.38 (0.35–0.41)
Total <sup>c</sup>	25,497	5,099	6	100.0	6.23 (6.15–6.30)	12,780	2,556	6.11 (6.00–6.22)	12,717	2,543	6.35 (6.24–6.46)
<sup>a</sup> Rates are per 100,000. <sup>b</sup> CBTRUS defines the broad category	of aliomas to inc	clude ICD-O-	-3 histopatho	loav codes 9	3380–9384, 9391–9460	. 9480.					

<sup>c</sup>Includes histopathologies not listed in this table. Abbreviations: CBTRUS, Central Brain Tumor Registry of the United States; NPCR, National Program of Cancer Registries; SEER, Surveillance, Epidemiology and End Results Program; Cl, confidence interval; NOS, not otherwise specified; ATRT, Atypical teratoid/rhabdoid tumor.

Oncology Neuro-

Histopathology	<1 yea	۲.			1–4 ye	irs		2-6	) years			10-14 years			15–19 year	S		
	Total Cases (2014- 2018)	Annual Average	% of All   * Cases in Age Group	Rate (95% Cl)	Total Cases (2014– 2018)	Annual <sup>9</sup> Average C i	6 of All F Cases n Age Group	late (95% Cl) Tot Ca: (20	al An ses Av 14- 18)	nual % of A erage Cases in Age Group	II Rate (95% Cl)	Total Anni Cases Aver (2014– 2018)	al % of/ age Casee in Age Group	All Rate (95% Cl)	Total A Cases A (2014– 2018)	nnual % verage Ca in Gı	of All Rate (95% ises Age oup	CI)
Gliomas <sup>b</sup>	458	92	4.0%	2.34 (2.13–2.57)	2,824	565 2	4.6% 3	3.55 (3.42–3.68) 3,0	19 60	t 26.3%	2.97 (2.86–3.08)	2,822 564	24.6%	2.73 (2.63–2.83)	2,351 47	70 20	.5% 2.23 (2.14-	-2.33)
Pilocytic astrocytoma	92	18	2.4% (	0.47 (0.38-0.58)	1,135	227 2	9.3% 1	.43 (1.34–1.51) 1,1	09 22	28.6%	1.09 (1.03–1.16)	914 183	23.6%	0.88 (0.83-0.94)	627 12	25 16	:2% 0.60 (0.55	-0.64)
Other Low grade gliom	a 142	28	6.6% (	0.73 (0.61–0.86)	347	69 1	6.0% (	0.44 (0.39–0.48) 416	83	19.2%	0.41 (0.37–0.45)	616 123	28.5%	0.60 (0.55-0.65)	643 12	29 29	1.7% 0.61 (0.56	-0.66)
High grade glioma	84	17	3.6% (	0.43 (0.34-0.53)	388	78 1	6.4% (	0.49 (0.44–0.54) 763	15	32.3%	0.75 (0.70–0.81)	603 121	25.5%	0.58 (0.54-0.63)	523 10	J5 22	2% 0.50 (0.46	-0.54)
Other glioma	75	15	1.1% (	0.38 (0.30–0.48)	574	115 8	3.3% (	0.72 (0.66–0.78) 534	101	7.7%	0.52 (0.48–0.57)	469 94	6.7%	0.45 (0.41–0.50)	332 66	6 4.8	8% 0.32 (0.28	-0.35)
Ependymal tumors	64	13	5.4% (	0.33 (0.25–0.42)	392	78 3	33.3% (	0.49 (0.44–0.54) 242	2 48	20.6%	0.24 (0.21-0.27)	243 49	20.7%	0.24 (0.21–0.27)	235 47	7 20	.0% 0.22 (0.20	-0.25)
Choroid plexus tumors	123	25	29.6% (	0.63 (0.52–0.75)	138	28	33.2% (	0.17 (0.15–0.20) 51	10	12.3%	0.05 (0.04–0.07)	57 11	13.7%	0.06 (0.04-0.07)	47 9	11	.3% 0.04 (0.03	-0.06)
Neuronal and mixed neuronal-glial tumors	31	9	2.4% (	0.16 (0.11–0.22)	162	32 1	12.6% 0	0.20 (0.17–0.24) 237	7 47	18.5%	0.23 (0.20–0.26)	404 81	31.5%	0.39 (0.35–0.43)	448 90	0 34	.9% 0.43 (0.39	-0.47)
Tumors of the pineal region	<16	1			49	10	3.0% 0	0.06 (0.05–0.08) 51	10	23.9%	0.05 (0.04–0.07)	1	:	I	66 13	31	.0% 0.06 (0.05	-0.08)
Embryonal tumors	257	51	10.7%	1.31 (1.16–1.48)	808	162 3	33.7% 1	.01 (0.95–1.09) 731	14(	30.5%	0.72 (0.67–0.77)	400 80	16.7%	0.39 (0.35-0.43)	201 40	0 8.	4% 0.19 (0.17-	-0.22)
Medulloblastoma	45	6	2.7% (	0.23 (0.17-0.31)	469	94 2	28.2% (	0.59 (0.54–0.64) 637	7 12	/ 38.3%	0.63 (0.58–0.68)	345 69	20.8%	0.33 (0.30-0.37)	166 33	3 10	.0% 0.16 (0.13	-0.18)
ATRT	143	29	37.3% (	0.73 (0.62–0.86)	190	38 2	19.6% (	0.24 (0.21–0.28) 32	9	8.4%	0.03 (0.02–0.04)	<16	1	;	<16	1	:	
Other embryonal tumo.	rs 69	14	19.6% (	0.35 (0.27–0.45)	149	30 2	12.3% 0	0.19 (0.16–0.22) 62	12	17.6%	0.06 (0.05–0.08)	<16	;	1	<16	1	;	
Tumors of cranial and spinal nerves	35	٢	2.9% (	0.18 (0.12–0.25)	220	44	18.3% (	).28 (0.24–0.32) 206	6 41	17.1%	0.20 (0.18–0.23)	287 57	23.9%	0.28 (0.25–0.31)	454 91	1 37	.8% 0.43 (0.39	-0.47)
Tumors of meninges	104	21	8.1% (	0.53 (0.43–0.64)	147	29 1	1.4% (	0.18 (0.16–0.22) 156	31	12.1%	0.15 (0.13–0.18)	291 58	22.5%	0.28 (0.25–0.32)	593 11	19 45	.9% 0.56 (0.52	-0.61)
Lymphomas and hema topoietic neoplasms	- <16	1			I			- 34	7	25.2%	0.03 (0.02–0.05)	35 7	25.9%	0.03 (0.02–0.05)	47 9	34	.8% 0.04 (0.03	-0.06)
Germ cell tumors	62	12	7.3% (	0.32 (0.24–0.41)	47	9	.5% 0	0.06 (0.04–0.08) 156	31	18.4%	0.15 (0.13–0.18)	318 64	37.5%	0.31 (0.27–0.34)	266 53	3 31	.3% 0.25 (0.22	-0.29)
Tumors of sellar region	21	4	0.5% (	0.11 (0.07–0.16)	173	35 3	.9% 0	0.22 (0.19–0.25) 612	2 12:	2 13.6%	0.60 (0.55–0.65)	965 193	21.5%	0.93 (0.88-0.99)	2,713 54	43 60	.5% 2.58 (2.48	-2.68)
Tumors of the pituitary	<16	I	I	1	ı	1		- 306	3 62	8.5%	0.30 (0.27–0.34)	740 148	20.3%	0.72 (0.67–0.77)	2,543 50	69 60	.9% 2.42 (2.32	-2.51)
Craniopharyngioma	<16	I	'	1	I	1		- 307	1 61	36.0%	0.30 (0.27–0.33)	225 45	26.6%	0.22 (0.19–0.25)	170 34	4 20	.1% 0.16 (0.14	-0.19)
<b>Unclassified Tumors</b>	131	26	8.3% (	0.67 (0.56–0.79)	244	49 1	5.5% (	.31 (0.27–0.35) 314	t 63	20.0%	0.31 (0.28-0.34)	409 82	26.1%	0.40 (0.36-0.44)	472 94	4 30	.1% 0.45 (0.41	-0.49)
Total <sup>c</sup>	1,235	247	4.8% (	5.31 (5.96–6.67)	4,871	974 1	9.1%	).12 (5.95–6.29) 5,6	28 1,1	26 22.1%	5.53 (5.39–5.68)	6,074 1,21!	5 23.8%	5.88 (5.73–6.03)	7,689 1,	538 30	.2% 7.31 (7.14–	7.47)
"Rates are per 100,000. "CBTRUS defines the broa "Includes histopathologies Data are not presented wr can be back-calculated us Abbreviations: CBTRUS, C Enidemiolonv and Ford Bas	d catego not liste ien fewe ing a cel entral Br	rry of gliom ed in this ta r than 16 c II. Suppres: ain Tumor I	ias to inclu ible. ases were sed cases Registry of	de ICD-0-3 histo reported for the are included in t f the United Stat	patholog specific be total ( ss; Cl, co	y codes 938 category. A count. nfidence int	0-9384, 9 verage a :erval; CD	391–9460, 9480. nnual counts and as: C, Centers for Disea:	sociated se Contro	ates cannot and Preven	be provided when to tion; NCI, National C	tal cases (201 ancer Institut	4–2018) ar	s fewer than 16 cases ational Program of Ca	or when a v	value base rries; SEER,	d on less than 16 Surveillance,	cases

Table 3. Annual Average Age-Specific Incidence Rates<sup>a</sup> for Childhood Brain and Other Central Nervous System Tumors Ages 0–19 Years by Major Histopathology Groupings, Histopathology, and Age Groups,

 Table 4.
 Annual Average Total<sup>a</sup>, Age-Specific Incidence Rates<sup>b</sup>, and One-, Five-, Ten-, and Fifteen-Year Relative Survival with 95% Confidence

 Intervals for High Grade Glioma in the Brain Stem<sup>c</sup> Ages 0–19 Years by Sex, Age Groups, Race, and Hispanic Ethnicity, (CBTRUS: Incidence Data provided by CDC's NPCR and NCI's SEER Program, 2014–2018; Survival Data provided by CDC's NPCR Program, 2001–2017)

Group	Incidence		Relative Survival			
	Annual Average Cases	Rate (95% CI)	1-year RS (95% CI)	5-year RS (95% CI)	10-year RS (95% CI)	15-year RS (95% CI)
Sex						
Male	136	0.33 (0.30–0.35)	63.2 (61.0–65.3)	39.6 (37.3–41.9)	38.1 (35.7–40.4)	37.3 (34.9–39.8)
Female	149	0.37 (0.34–0.40)	59.9 (57.7–62.0)	35.1 (32.9–37.3)	33.3 (31.1–35.5)	32.9 (30.6–35.1)
Age						
<1 year	6	0.15 (0.10–0.22)	80.5 (69.4–87.9)	75.8 (64.0–84.2)	73.6 (61.1–82.6)	73.6 (61.1–82.6)
1–4 years	61	0.38 (0.34–0.43)	62.1 (58.9–65.1)	32.3 (29.2–35.4)	29.9 (26.8–33.1)	28.4 (25.2–31.7)
5–9 years	115	0.56 (0.52–0.61)	49.4 (47.0–51.9)	25.1 (22.9–27.3)	24.2 (22.0–26.5)	24.0 (21.7–26.3)
10–14 years	67	0.33 (0.29–0.36)	73.4 (70.2–76.3)	51.7 (48.1–55.2)	50.4 (46.7–54)	50.1 (46.3–53.8)
15–19 years	36	0.17 (0.15–0.20)	79.6 (75.4–83.1)	60.8 (55.8–65.4)	56.9 (51.5–61.9)	56.9 (51.5–61.9)
Race						
White	211	0.34 (0.32–0.36)	62.2 (60.4–63.9)	39.1 (37.3–41.0)	37.4 (35.5–39.3)	36.8 (34.9–38.7)
Black	52	0.38 (0.34–0.43)	57.6 (53.7–61.3)	29.2 (25.6–32.9)	27.1 (23.5–30.9)	26.6 (22.8–30.5)
American Indian/ Alaska Native	' <16 total cases from 2014–2018	<16 total cases from 2014–2018	< 50 cases	< 50 cases	< 50 cases	< 50 cases
Asian or Pacific Islander	13	0.26 (0.20–0.33)	57.5 (49.5–64.6)	31.7 (24.5–39.2)	30.8 (23.6–38.3)	30.8 (23.6–38.3)
Ethnicity						
Non-Hispanic	228	0.37 (0.35–0.39)	63.5 (61.7–65.1)	39.3 (37.4–41.1)	37.7 (35.8–39.5)	37 (35.1–38.9)
Hispanic	56	0.28 (0.25–0.31)	54.2 (50.8–57.6)	30.1 (26.9–33.4)	28.0 (24.7–31.4)	27.7 (24.4–31.1)
Total	285	0.35 (0.33–0.37)	61.5 (59.9–63.0)	37.3 (35.7–38.9)	35.6 (34.0–37.3)	35.1 (33.4–36.7)

<sup>a</sup>Annual average cases are calculated by dividing the five-year total by five.

<sup>b</sup>Rates are per 100,000.

°ICD-0-3 site code C71.7 and ICD-0-3 morphology codes 9380, 9381, 9400, 9401, 9440, 9441, 9442/3, 9451, 9460 (See Supplementary Tables 1 and 2 for more information).

Incidence data are not presented when fewer than 16 cases were reported for the specific category and survival data is not presented when fewer than 50 cases were reported for the specific category.

Abbreviations: CBTRUS, Central Brain Tumor Registry of the United States; CI, confidence interval; NOS, not otherwise specified; CDC, Centers for Disease Control and Prevention; NCI, National Cancer Institute; NPCR, National Program of Cancer Registries; RS, Relative Survival; SEER, Surveillance, Epidemiology and End Results Program.

- In infants (< 1 year of age), the site with the highest incidence was brain, NOS (1.07 per 100,000). This may refer to the pons (which does not have a specific location code in the ICD-O-3 system) or to tumors that were otherwise not able to be biopsied. The second most frequently occurring site was the ventricle (1.05 per 100,000).</li>
- In children 1–4 years, the most common occurring site was the cerebellum (1.23 per 100,000), followed by the optic nerve (0.85 per 100,000).
- In children 5–9 years, the site with highest incidence was cerebellum (1.12 per 100,000), followed by the brain stem (0.86 per 100,000).
- In children 10–14 years, the sites with highest incidence were the pituitary gland (0.79 per 100,000) and the cerebellum (0.56 per 100,000).
- In adolescents 15–19 years, the sites with highest incidence were the pituitary gland (2.50 per 100,000) and the temporal lobe (0.54 per 100,000).

### Median Age at Diagnosis

The median age at diagnosis for all primary brain and other CNS tumors among children and adolescents ages 0–19 years was 9 years old (Table 2).

- The histopathology-specific median ages ranged from 1 year for ATRT to 16 years for tumors of the sellar region and subtype tumors of the pituitary.
- Choroid plexus tumors, embryonal tumors, ATRT, and other embryonal tumors were histopathologies with median age < 6 years of age at diagnosis.
- ATRT and other embryonal tumors were primarily diagnosed in infants and children 0–9 years of age at diagnosis, while tumors of the pineal region, lymphomas and hematopoietic neoplasms, tumors of the pituitary, and craniopharyngioma were rarely diagnosed in infants < 1 year of age.</li>

Neuro-Oncology

lumor Keport: NI	CK and S	SEER, 20	14-2018													
Site	0–19 ye	ars	V	<1 year		÷	-4 years			5-9 year	s	10–14 y	ears	15-1	9 years	
	Total Cases (2014– 2018)	Annua Averaç	Rate (95% Cl)    e	Total Cases (2014– 2018)	Annual Averag	Rate (95% Cl) T e (5 2	otal ases 2014– 018)	Annual Rate (95 Average	% CI)	Total Cases (2014– 2018)	Annual Rate (95% Average	CI) Total Cases (2014– 2018)	Annual Average	Rate (95% Cl) Tota Case (2011	l Annual es Averagi 4-	Rate (95% Cl)
Frontal, temporal, parietal, and occipii lobes of the brain	4,128 :al	826	1.01 (0.98–1.04)	153	31	0.78 (0.66–0.92) 6	06	121 0.76 (0.7	(0-0.82)	712	142 0.70 (0.65	-0.75) 1,234	247	1.19 (1.13–1.26) 1,42	3 285	1.35 (1.28–1.42)
Frontal lobe	1,499	300	0.37 (0.35–0.39)	19	10	0.25 (0.19–0.33) 2	07	41 0.26 (0.2	(3-0.30)	241	48 0.24 (0.21	-0.27) 450	90	0.44 (0.40-0.48) 552	110	0.52 (0.48–0.57)
Temporal lobe	1,687	337	0.41 (0.39–0.43) E	29	12	0.30 (0.23–0.39) 2	56	51 0.32 (0.2	8-0.36)	293	59	-0.32) 507	101	0.49 (0.45–0.54) 572	114	0.54 (0.50-0.59)
Parietal lobe	649	130	0.16 (0.15–0.17) 2	28	9	0.14 (0.10-0.21) 1	15	23 0.14 (0.1	2-0.17)	127	25 0.12 (0.10	-0.15) 190	38	0.18 (0.16–0.21) 189	38	0.18 (0.15–0.21)
Occipital lobe	293	59	0.07 (0.06–0.08) 1	17	e	0.09 (0.05–0.14) 2	00	6 0.04 (0.0	12-0.05	51	10 0.05 (0.04	-0.07) 87	17	0.08 (0.07–0.10) 110	22	0.10 (0.09–0.13)
Cerebrum	1,375	275	0.34 (0.32–0.35) 7	11	14	0.36 (0.28–0.46) 2	60	52 0.33 (0.2	9-0.37)	363	73 0.36 (0.32	-0.40) 389	78	0.38 (0.34–0.42) 292	58	0.28 (0.25–0.31)
Ventricle	1,333	267	0.33 (0.31–0.34) 2	205	41	1.05 (0.91–1.20) 3:	30	66 0.41 (0.3	87–0.46)	241	48 0.24 (0.21	-0.27) 285	57	0.28 (0.24–0.31) 272	54	0.26 (0.23–0.29)
Cerebellum	3,635	727	0.89 (0.86–0.92) 1	124	25	0.63 (0.53-0.76) 9	80	196 1.23 (1.1	6–1.31)	1,138	228 1.12 (1.05-	-1.19) 803	161	0.78 (0.72-0.83) 590	118	0.56 (0.52–0.61)
Brain stem	2,562	512	0.63 (0.60–0.65) §	66	20	0.51 (0.41–0.62) 6	42	128 0.81 (0.7	5-0.87)	877	175 0.86 (0.81	-0.92) 581	116	0.56 (0.52-0.61) 363	73	0.34 (0.31–0.38)
Other brain	2,926	585	0.71 (0.69–0.74)	271	54	1.38 (1.22–1.56) 6	63	133 0.83 (0.7	(06:0-2	703	141 0.69 (0.64	-0.74) 703	141	0.68 (0.63-0.73) 586	117	0.56 (0.51–0.60)
Overlapping lesi of brain	on720	144	0.18 (0.16–0.19)	32	12	0.32 (0.24–0.41) 14	41	28 0.18 (0.1	5-0.21)	163	33 0.16 (0.14	-0.19) 190	38	0.18 (0.16–0.21) 164	33	0.16 (0.13–0.18)
Brain, NOS	2,206	441	0.54 (0.52–0.56) 2	209	42	1.07 (0.93–1.22) 5:	22	104 0.66 (0.6	60-0.71)	540	108 0.53 (0.49	-0.58) 513	103	0.50 (0.45–0.54) 422	84	0.40 (0.36–0.44)
Spinal cord and cauda equina	1,330	266	0.32 (0.31–0.34) 1	112	22	0.57 (0.47–0.69) 2	68	54 0.34 (0.3	t0-0.38)	222	44 0.22 (0.19	-0.25) 331	66	0.32 (0.29–0.36) 397	79	0.38 (0.34–0.42)
Cranial nerves	1,859	372	0.45 (0.43–0.48) 8	32	16	0.42 (0.33–0.52) 6	66	140 0.88 (0.8	81–0.95)	448	90 0.44 (0.40	-0.48) 307	61	0.30 (0.26–0.33) 323	65	0.31 (0.27–0.34)
Olfactory nerve	<16 cases	1	1	<16 cases	I	1	.16 ases	1		<16 cases	1	<16 cases	ı	<16 case	I S	I
Optic nerve	1,371	274	0.33 (0.32–0.35) 7	73	15	0.37 (0.29–0.47) 6	76	135 0.85 (0.7	'9–0.92)	382	76 0.38 (0.34	-0.42) 157	31	0.15 (0.13–0.18) 83	17	0.08 (0.06–0.10)
Acoustic nerve	288	28	0.07 (0.06–0.08) <	<16 case		1	.16 ases	1			1	87	17	0.08 (0.07–0.10) 159	32	0.15 (0.13–0.18)
Cranial nerve, NC	797 J97	39	0.05 (0.04-0.06)	<16 case	-s		7	3 0.02 (0.0	1-0.03)	33	7 0.03 (0.02	-0.05)	1	-	I	I
Other nervous system	382	76	0.09 (0.08–0.10)	40	00	0.20 (0.15–0.28) 1:	35	27 0.17 (0.1	4-0.20)	33	0.09 (0.07	-0.11) 51	10	0.05 (0.04–0.06) 63	13	0.06 (0.05–0.08)
Meninges	738	148	0.18 (0.17–0.19) 3	33	7	0.17 (0.12–0.24) 6	0	12 0.08 (0.0	6-0.10)	94	19 0.09 (0.07	-0.11) 175	35	0.17 (0.15-0.20) 376	75	0.36 (0.32–0.40)
Pituitary and craniopharyngeal duct	4,508	902	1.10 (1.07–1.13)	53	വ	0.12 (0.07–0.18) 1	59	32 0.20 (0.7	7-0.23)	603	121 0.59 (0.55	-0.64) 979	196	0.95 (0.89–1.01) 2,74	4 549	2.61 (2.51–2.71)
Pituitary gland	3,896	779	0.95 (0.92–0.98) -		ı	-		1		365	73 0.36 (0.32	-0.40) 821	164	0.79 (0.74–0.85) 2,62	8 526	2.50 (2.40–2.59)
Craniopharynges duct	<i>l</i> 612	122	0.15 (0.14–0.16) <	<16 case	5	1		1		238	48 0.23 (0.21	-0.27) 158	32	0.15 (0.13–0.18) 116	23	0.11 (0.09–0.13)

Table 5. Annual Average Age-Specific Incidence Rates<sup>a</sup> for Childhood Brain and Other Central Nervous System Tumors Ages 0–19 Years by Site<sup>b</sup> and Age Groups, CBTRUS Childhood and Adolescent Brain

Site	0–19 ye	ars		<1 year			1–4 year	s		5-9 year	(A)		10–14 yea	ırs	-	5-19 уеа	ars	
	Total Cases (2014– 2018)	Annual Average	Rate (95% Cl)	Total Cases (2014– 2018)	Annual Average	Rate (95% Cl)	Total Cases (2014– 2018)	Annual Average	Rate (95% CI)	Total Cases (2014– 2018)	Annual Average	Rate (95% CI)	fotal Cases 2014– 2018)	Annual Average	Rate (95% Cl) 7 C (1	otal / ases / 2014- (018)	Annual Average	3ate (95% Cl)
Pineal gland	869	140	0.17 (0.16–0.18)	22	4	0.11 (0.07–0.17)	69	14	0.09 (0.07–0.11)	133	27	0.13 (0.11–0.15)	229	46	0.22 (0.19–0.25) 2	45 4	19	0.23 (0.20–0.26)
Olfactory tumors of the nasal cavity <sup>c</sup>	53	ъ	0.01 (0.00–0.01)	<16 cases	ı	1	<16 cases	;	1	<16 cases		1	<16 cases	1	1	ases -		
Total	25,497	5,099	6.23 (6.15–6.30)	1,235	247	6.31 (5.96–6.67)	4,871	974	6.12 (5.95–6.29)	5,628	1,126	5.53 (5.39–5.68)	3,074	1,215	5.88 (5.73–6.03) 7,	. 689	1,538	7.31 (7.14–7.47)
8D atra are are 100 000																		

validation list site/histology in the SEER on the categories and site codes defined based sites referred to in this table are loosely

CD-0-3 histology codes 9522–9523 only

based on less than 16 cases when a value fewer than 16 cases or are 1 (2014 - 2018)cases when total annual counts and associated rates cannot be provided Average reported for the specific category. count. total ( included in the arei than 16 cases were . Suppressed cases Data are not presented when fewer

confidence interval; CDC, Centers for Disease Control and Prevention; NCI, National Cancer Institute, NPCR, National Program of Cancer Registries; SEER, Surveillance States; CI, of the United Registry **Brain Tumor** CBTRUS, Central Brai End Results Program can be back-calculated using a cell. Abbreviations: CBTRUS, Central E and Epidemiology

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### Sex-, Race-, And Hispanic Ethnicity-Specific **Incidence Rates**

Distribution and Incidence by Sex, Behavior, and Histopathology- Overall incidence of primary brain and other CNS tumors by sex and behavior are shown in Table 1. Incidence rates, counts of total cases and annual average cases by sex and histopathology are shown in Table 2 and Figure 5, and are further stratified by age groups in Supplementary Table 4.

- Overall, 50.1% of all primary brain and other CNS tumors in children and adolescents diagnosed between 2014-2018 occurred in males (12,780 tumors) and 49,9% in females (12,717 tumors) (Table 2).
- Approximately 54.4% of the annual average malignant tumor cases occurred in males (1,584 tumors between 2014-2018) and 45.6% in females (1,326 tumors between 2014-2018) (Table 1).
- Incidence rates for all primary brain and other CNS tumors combined were higher among females (6.35 per 100,000) than males (6.11 per 100,000).
- Incidence was higher in males than females for histopathologies including other low-grade glioma (0.57 vs 0.49 per 100,000), ependymal tumors (0.32 vs 0.26 per 100,000), medulloblastoma (0.51 vs 0.30 per 100,000), and germ cell tumors (0.28 vs 0.13 per 100,000).
- Incidence was higher in females than males for tumors of the pituitary (1.34 vs 0.45 per 100,000).

Incidence Rates by Race, Behavior, and Histopathology-Overall incidence of primary brain and other CNS tumors by race and behavior are shown in Table 1. Incidence rates, counts of total cases and annual average cases by race and histopathology are shown in Table 6 and Figure 6, and are further stratified by age groups in Supplementary Table 4.

- Incidence rates for all primary brain and other CNS tumors combined were lower for AIAN children and adolescents (3.31 per 100,000) compared to White children and adolescents (6.44 per 100,000), Black children and adolescents (4.88 per 100,000), and API (5.66 per 100,000) children and adolescents.
- Incidence rates for non-malignant primary brain and other CNS tumors were highest in White children and adolescents (2.75 per 100,000) compared to Black children and adolescents (2.15 per 100,000), AIAN children and adolescents (1.52 per 100,000), and API (2.40 per 100,000) children and adolescents.
- Incidence rates for malignant primary brain and other CNS tumors were highest in White children and adolescents (3.69 per 100,000), compared to Black children and adolescents (2.73 per 100,000), AIAN children and adolescents (1.79 per 100,000), and API (3.26 per 100,000) children and adolescents.
- · AIAN children and adolescents had lowest incidence in all histopathology groups. This may reflect differences in access to diagnostic care.
- · Incidence of embryonal tumors, medulloblastoma, ATRT, tumors of cranial and spinal nerves, lymphomas



Fig. 5 Incidence Rates and Incidence Rate Ratios (IRR) with 95% Confidence Intervals by Sex for Selected Primary Brain and Other Central Nervous System Tumor Histopathologies in Children and Adolescents Ages 0–19 Years, CBTRUS Childhood and Adolescent Report: US Cancer Statistics—NPCR and SEER, 2014–2018.

and hematopoietic neoplasms, and germ cell tumors observed for API children and adolescents exceeded those observed for White, Black, and AIAN children and adolescents.

 While there are histopathologies where significant differences in incidence were observed by race, in most cases the actual difference in incidence races is small and may not be biologically significant.

Incidence Rates by Hispanic Ethnicity, Behavior, and Histopathology.— Incidence rates by Hispanic ethnicity and histopathology are shown in Table 1. Incidence counts of total cases, average annual age-specific rates, and incidence rate ratios by Hispanic ethnicity and histopathology are shown in Table 6 and Figure 7.

- The overall incidence rate for primary brain and other CNS tumors in children and adolescents was 6.52 per 100,000 population among non-Hispanic children and adolescents and 5.33 per 100,000 population among their Hispanic counterparts.
- Tumors of the sellar region and tumors of the pituitary were the only histopathologies that were higher in Hispanic than in non-Hispanics children and adolescents.
- While there were histopathologies where significant differences in incidence were observed by Hispanic

ethnicity, in most cases the actual difference in incidence rates is small and may not be biologically significant.

### Frequency of and Incidence of Molecularly-Defined Brain and Other CNS Tumor Histopathologies

Beginning in diagnosis year 2018, US cancer registry systems began collecting data on molecularly defined histopathologies introduced in the *2016 WHO classification of tumours of the CNS*, including *IDH*1/2 mutation and 1p/19q codeletion status for adult-type diffuse glioma, and medulloblastoma subtypes. Total cases of these histopathologies diagnosed in 2018–2019, age-specific incidence rates, median age of diagnosis, and distribution by sex and race/ethnicity are shown in Table 7.

- While adult-type diffuse glioma is rare in children and adolescents, *IDH1/2* - mutant astrocytoma had an incidence rate of 0.09 per 100,000 population, while *IDH1/2* - wildtype astrocytoma had an incidence rate of 0.17 per 100,000 population. Median age of diagnosis for these subtypes was 15 and 10 years, respectively.
- The most common medulloblastoma subtype is non-WNT/non-SHH, which had an incidence rate of 0.08 per 100,000 population and a median age of

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nd Other Central	118
Rates <sup>a</sup> for Brain a	nd SEER, 2014–20
pecific Incidence	nt Report: NPCR a
I Average Age-Sp	od and Adolesce
Table 6. Annua	<b>CBTRUS</b> Childho

Histopathology	White			Black			AIAN		API		Hispai	lic		Von-Hispa	anic	
	Total Case (2014–2018	s Annual 8) Averag	l Rate (95% Cl) je	Total Cases (2014– 2018)	Annual Averag	I Rate (95% CI) je	Total Cases Ar (2014–2018) Av	nnual Rate (95% Cl erage	) Total / Cases / (2014- 2018)	Annual Rate (95% Average	6 Cl) Total Cases (2014- 2018)	Annual Average	Rate (95% Cl)	fotal Ar Cases Ar 2014- 2018)	nual Ra erage	(te (95% Cl)
Gliomas°	9,068	1,814	2.94 (2.88–3.00)	1,471	294	2.16 (2.05–2.27)	103 21	1.35 (1.10–1.6	4) 576 1	115 2.26 (2.08	3-2.45) 2,092	418	2.08 (1.99–2.17) 5	9,382 1,8	376 3.	04 (2.98–3.10)
Pilocytic astrocytoma	3,118	624	1.01 (0.98–1.05)	461	92	0.68 (0.62-0.74)	36 7	0.47 (0.33–0.	35) 178 3	36 0.70 (0.60	)-0.81) 679	136	0.67 (0.62-0.73) 3	3,198 64	0 1.(	14 (1.00–1.07)
Other Low grade glioma	1,699	340	0.55 (0.53–0.58)	277	55	0.41 (0.36–0.46)	25 5	0.33 (0.21–0.	118 2	24 0.46 (0.35	3-0.55) 362	72	0.36 (0.32–0.40)	1,802 36	0.	58 (0.56–0.61)
High grade glioma	1,801	360	0.58 (0.56–0.61)	379	76	0.56 (0.50-0.61)	21 4	0.27 (0.17–0.	12) 118 2	24 0.46 (0.35	}−0.55) 475	95	0.47 (0.43-0.52) 1	1,886 37	7 0.	31 (0.58–0.64)
Other glioma	1,580	316	0.51 (0.49–0.54)	215	43	0.32 (0.27-0.36)	:	I	118 2	24 0.46 (0.36	1-0.55) 334	67	0.33 (0.30-0.37) 1	1,650 33	0.	53 (0.51–0.56)
Ependymal tumors	932	186	0.30 (0.28–0.32)	149	30	0.22 (0.18–0.26)	<16	ı	56 1	11 0.22 (0.17	7-0.29) 268	54	0.27 (0.24–0.30) §	908 18	2	29 (0.28–0.31)
Choroid plexus tumors	325	65	0.11 (0.09-0.12)	56	11	0.08 (0.06–0.11)	<16	1	20 4	1 0.08 (0.05	i-0.12) 92	18	0.09 (0.07-0.11)	324 65	0	10 (0.09–0.12)
Neuronal and mixed neuronal-glial tumors	1,010	202	0.33 (0.31–0.35)	172	34	0.25 (0.22–0.29)	<16 -	I	72 1	14 0.28 (0.23	2-0.36) 232	46	0.23 (0.20–0.26)	1,050 21	0	34 (0.32–0.36)
Tumors of the pineal region	140	28	0.05 (0.04–0.05)	53	7	0.08 (0.06–0.10)	<16 -	1	< 16	1	40	8	0.04 (0.03–0.05)	173 35	.0	06 (0.05–0.07)
Embryonal tumors	1,856	371	0.60 (0.58–0.63)	292	58	0.43 (0.38–0.48)	29 6	0.38 (0.25–0.	55) 159 3	32 0.62 (0.53	}−0.73) 520	104	0.52 (0.47-0.56) 1	1,877 37	5	31 (0.58–0.64)
Medulloblastoma	1,306	261	0.42 (0.40–0.45)	178	36	0.26 (0.22-0.30)	22 4	0.29 (0.18–0.4	115 2	23 0.45 (0.37	7-0.54) 349	70	0.35 (0.31-0.38) 1	1,313 26	.0	13 (0.40–0.45)
ATRT	281	56	0.09 (0.08–0.10)	58	12	0.09 (0.06–0.11)	<16	ı	;	:	82	16	0.08 (0.06–0.10) 3	301 60	.0	10 (0.09–0.11)
Other embryonal tumors	269	54	0.09 (0.08–0.10)	56	1	0.08 (0.06–0.11)	<16 -	1	< 16	1	88	18	0.09 (0.07–0.11)	263 53	.0	00 (0.08–0.10)
Tumors of cranial and spinal nerves	935	187	0.30 (0.28–0.32)	141	28	0.21 (0.17–0.24)	<16 -	I	79 1	16 0.31 (0.25	5-0.39) 242	48	0.24 (0.21–0.27) §	960 19	2	31 (0.29–0.33)
Tumors of meninges	1,013	203	0.33 (0.31-0.35)	169	34	0.25 (0.21-0.29)	<16	I	69	14 0.27 (0.21	-0.34) 296	59	0.29 (0.26-0.33) 5	95 19	9	32 (0.30–0.34)
Lymphomas and hema- topoietic neoplasms	- 97	19	0.03 (0.03–0.04)	16	e	0.02 (0.01–0.04)	<16 -	I	20 4	4 0.08 (0.0E	5-0.12) 22	4	0.02 (0.01–0.03)	113 23	.0	04 (0.03–0.04)
Germ cell tumors	643	129	0.21 (0.19–0.23)	06	18	0.13 (0.11–0.16)	<16	I	86 1	17 0.34 (0.27	-0.42) 213	43	0.21 (0.18-0.24) 6	336 12	7 0.	21 (0.1 <del>9-</del> 0.22)
Tumors of sellar region	3,405	681	1.10 (1.07–1.14)	654	131	0.96 (0.89–1.04)	52 10	0.68 (0.51–0.4	39) 240 4	18 0.94 (0.83	3-1.07) 1,228	246	1.22 (1.15–1.29) 🔅	3,256 65	1 1.0	15 (1.02–1.09)
Tumors of the pituita	۲ <i>y</i> 2,783	557	0.90 (0.87–0.94)	501	100	0.73 (0.67–0.80)	1	I	196 3	39 0.77 (0.67	7-0.89) 1,035	207	1.03 (0.97–1.09)	2,604 52	1.0	34 (0.81–0.88)
Craniopharyngioma	622	124	0.20 (0.19–0.22)	153	31	0.22 (0.19–0.26)	<16	I	44 5	9 0.17 (0.13	3-0.23) 193	39	0.19 (0.17-0.22) €	352 13	0	21 (0.20–0.23)
UnclassifiedTumors	1,228	246	0.40 (0.38–0.42)	192	38	0.28 (0.24–0.32)	18 4	0.24 (0.14–0.;	1 90 1	18 0.35 (0.26	3-0.43) 347	69	0.34 (0.31-0.38) 1	1,223 24	5.0.	10 (0.37–0.42)
Total <sup>d</sup>	19,854	3,971	6.44 (6.35–6.53)	3,326	665	4.88 (4.71–5.05)	253 51	3.31 (2.92–3.	75) 1,441 2	288 5.66 (5.37	-5.96) 5,367	1,073	5.33 (5.19–5.47) 2	20,130 4,0	026 6.1	52 (6.43–6.61)
<sup>a</sup> Rates are per 100,000.		10														

•CBTRUS defines the broad category of gliomas to include ICD-0.3 histopathology codes 9380-9384, 9391–9460, 9480.
•CBTRUS defines the broad category of gliomas to include ICD-0.3 histopathology codes 9380-9384, 9391–9460, 9480.
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•CBTRUS defines the broad category of gliomas to include ICD-0.3 histopathology codes 9380-9384, 9391–9460, 9480.
•CBTRUS defines the propertion of category of gliomas to include ICD-0.3 histopathology. Average annual counts and associated rates cannot be provided when Total Cases (2014–2018) are fewer than 16 cases or when a value based on less than 16 cases are included in the total count.
Abbreviations: CBTRUS, Central Brain Tumor Registry of the United States; NPCR, National Program of Cancer Registries; SEER, Surveillance, Epidemiology and End Results Program; CI, confidence interval, NOS, not otherwise specified; ATRT, Atypical teratoid/rhabdoid tumor.

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Oncology



Fig. 6 Incidence Rate and Incidence Rate Ratios (IRR) with 95% Confidence Intervals by Race for Selected Primary Brain and Other Central Nervous System Tumor Histopathologies in Children and Adolescents Ages 0–19 Years, CBTRUS Childhood and Adolescent Report: US Cancer Statistics—NPCR and SEER, 2014–2018.

diagnosis of 7 years. SHH-activated & *TP53* - wildtype medulloblastoma was the second most commonly occurring subtype, with an incidence rate of 0.05 per 100,000 and a median age of diagnosis of 4.5 years. Incidence of WNT-activated medulloblastoma was 0.02 per 100,000 population, with median age of diagnosis of 9 years. SHH-activated and *TP53*-mutant medulloblastoma was too rare to calculate incidence.

- Molecular subtype data was missing for many medulloblastoma cases, but the completeness of these data are expected to increase in future years.
- Embryonal tumor with multilayered rosettes, C19MCaltered had an incidence rate of 0.02 per 100,000 population and a median age of diagnosis of 2 years.
- Diffuse midline glioma, H3 K27M-mutant had an incidence rate of 0.12 per 100,000 population and a median age of diagnosis of 8 years.

### Incidence Time Trends

Time trends in cancer incidence are important measures of the changing burden of cancer in a population over time. Many factors may lead to fluctuations in rates over time, and all of these must be considered when interpreting time trends results. When assessing trends in incidence over time it is critical to use the most recent data available, as delays in reporting may cause small fluctuations in incidence. Time trends analysis methods are used to estimate if the annual percentage change (APC) is significantly different from 0% (meaning no change in incidence from year to year). In addition to assessing statistical significance of changes in incidence over time, the size of this change must also be considered because with datasets as large as CBTRUS very small fluctuations in incidence over time may be statistically significant but not truly represent a large change in proportion of individuals over time.

Annual age-specific incidence rates and APC for all primary brain and other CNS tumors in comparison to other common childhood and adolescent cancers are shown in Figure 8.

- Overall, incidence of all primary malignant and nonmalignant brain and other CNS tumors increased significantly from 2004 to 2013 (APC = 2.1%; 95% Cl: 1.6% - 2.7%), followed by relatively stable incidence after 2013.
- Incidence of leukemia increased slightly over the entire period (APC = 0.5%, 95%CI: 0.1%-0.8%).
- Incidence of lymphoma increased from 2004–2015 (APC = 2.2%, 95%CI: 1.6%-2.9%), but was stable thereafter.





 Incidence of malignant bone tumors, soft tissue tumors, and non-CNS germ cell tumors remained stable across the entire period.

Annual age-specific incidence rates and APC for selected histopathologies overall and by age groups are shown in Figure 9. Complete APC results are available in Supplementary Table 7.

- Incidence of pilocytic astrocytoma increased significantly from 2004 to 2018 (APC = 1.2%; 95%Cl = 0.5% -1.9%). This increase was highest in infants 0–3 years old, where APC was 2.9% (95%Cl: 1.9% - 4.0%)
- High grade glioma incidence increased slightly, but significantly from 2004 to 2016 (APC = 2.1%; 95%Cl: 1.2% 3.1%).
- There was a significant increase in incidence of tumors of the pituitary from 2004 to 2012 (APC = 7.2%; 95%Cl: 4.8% - 9.7%) followed by relatively stable incidence after 2012.
- The increases in incidence in tumors frequently diagnosed by imaging alone, such as tumors of the pituitary, are partially attributable to improved collection of radiographically diagnosed cases as well as improvement in collection of non-malignant cases in general over time.

### Age-, Sex-, Race-, Ethnicity- and State-Specific Brain Tumor Mortality Rates

Age-specific mortality rates for primary malignant brain and other CNS tumors in the United States during 2014–2018 overall, by sex, race, Hispanic ethnicity, age groups and state are shown in Table 1, Figure 10, and Supplementary Table 4.

- Mortality due to primary malignant brain tumors was higher in males as compared to females (0.71 per 100,000 as compared to 0.60 per 100,000).
- Children ages 5–9 years had the highest mortality of any age group (0.93 per 100,000).
- Mortality was highest in White (0.68 per 100,000) and Black (0.65 per 100,000) children and adolescents as compared to other racial groups.
- Non-Hispanic children and adolescents had higher mortality as compared to Hispanic children and adolescents (0.68 per 100,000 as compared to 0.60 per 100,000).
- Mortality due to primary malignant brain and CNS tumors varied by state, from a minimum of 0.33 per 100,000 to 1.50 per 100,000 population.

Tumor type	ICD-O-3 histopathology codes	Total New Cases	Rate (95% Cl)	Age (median, in- terquartile range)	Female (%)	Non-Hispanic White (%)	Non- Hispanic Block 1023	Hispanic (%)
							DIGCN 1/01	
Adult-type diffuse glioma								
IDH1/2 - mutant Astrocytoma <sup>b</sup>	9400/3, 9401/3, 9445/3	142	0.09 (0.07–0.10)	15 (8.75–18)	45.8	70.4	I	16.2
IDH1/2 - wildtype Astrocytoma and Glioblastoma <sup>c</sup>	9400/3, 9401/3, 9440/3	279	0.17 (0.15–0.19)	10 (6–15)	43.0	67.7	10.0	16.5
IDH1/2 mutant & 1p/19q-codeleted Oligodendroglioma <sup>d</sup>	9450/3, 9451/3	34	0.02 (0.01–0.03)	15 (9.5–18)	I	82.4	ł	ł
Medulloblastoma								
SHH-activated & TP53 wildtype <sup>e</sup>	9471/3	80	0.05 (0.04–0.06)	4.5 (2–9.25)	31.3	51.2	ł	21.2
SHH-activated & TP53 mutant	9476/3	< 16 cases	ł	I	ł	I	I	ł
WNT-activated	9475/3	25	0.02 (0.01–0.02)	9 (7–11)	ł	72.0	1	I
nonWNT/nonSHH	9477/3	122	0.08 (0.06–0.09)	7 (4–10)	34.4	63.1	1	26.2
Other tumor types								
Embryonal tumor with multilayered ros- ettes, C19MC-altered <sup>f</sup>	9478/3	25	0.02 (0.01–0.02)	2 (1–3)		I	I	I
Ependymoma, RELA fusion	9396/3	< 16 cases	1	I		I	1	I
Diffuse midline glioma, H3 K27M- mutant	9385/3	197	0.12 (0.11–0.14)	8 (5–12)	59.9	49.2	11.7	27.9
Pilomyxoid astrocytoma	9425/3	40	0.02 (0.02–0.03)	3 (1–7)	45.0	72.5	I	I
<sup>a</sup> Rates are per 100,000. <sup>b</sup> ICD-0-3 histopathology code of 9400/3, 9401/3 ar <sup>b</sup> ICD-0-3 histopathology code of 9450/3, 9451/3 ar <sup>c</sup> ICD-0-3 histopathology code of 9471/3 and a BM <sup>d</sup> ICD-0-3 histopathology code of 9478/3 and a BM <sup>f</sup> ICD-0-3 histopathology code of 9478/3 and a BM <sup>f</sup> ICD-0-3 histopathology code of 9478/3 and a Case <sup>d</sup> ICD-0-3 histopathology code of 9478/3 and a BM <sup>f</sup> ICD-0-4 and 10 f a second and 10 f a second <i>c</i> Abbreviations: BMM, brain molecular ma	nd a BMM value of 1 or 3, or I( 9440/3 and a BMM value of 2, 4 nd a BMM of 6 or7. AM value of 8. AM value of 9. s were reported for the speci ealculated using a cell. Suppre arkers variable: CBTRUS, utts Program: CI. confider	L-D-D-3 histopathol L, or 5. fic category. Count ssed cases are in <i>Central Brain Tu</i> <i>Central Brain Tu</i>	ogy code of 9445/3. s and associated rates cluded in the total coun mor Registry of the	cannot be provided wh t. United States; NPC	nen Total Case R, National	ss (2018–2019) are fer Program of Canc	wer than 16 case <i>er Registries;</i>	s or when a SEER,



Fig. 8 Annual Age-Specific Incidence Rates of All Primary Malignant and Non-Malignant Brain and Other Central Nervous System Tumors in Children and Adolescents Ages 0–19 Years, and Incidence Trends in Comparison to Other Common Childhood and Adolescent Cancers, CBTRUS Childhood and Adolescent Report: US Cancer Statistics—NPCR and SEER, 2004–2018.

### Mortality Time Trends

Time trends in cancer mortality are important measures of the changing burden of cancer in a population over time. **Many factors may lead to fluctuations in rates over time, and all of these must be considered when interpreting time trends.** When assessing trends in mortality over time it is critical to use the most recent data available, as delay in reporting may cause small fluctuations in incidence. Time trends analysis methods are used to estimate if the APC is significantly different from 0% (meaning no change in mortality from year to year).

Annual age-specific mortality rates and APC for selected major causes of cancer death as compared to brain and other CNS tumors from 1975 to 2018 are shown in Figure 11 and shown in Figure 12 for annual age-specific mortality rates and APC due to primary malignant brain and other CNS tumors by age groups. Complete APC results are available in SupplementaryTable 8.

- Overall, mortality due to cancer has decreased in children and adolescents ages 0–19 years since 1975.
- Some of the biggest decreases have come in leukemia, where mortality decreased by 4.4% per year from 1969 to 1984 (95% Cl: -4.7% -4.1%) and by 2.8% per year from 1984 to 2018 (95% Cl: -2.9% -2.7%).
- While mortality due to brain and other CNS tumors also decreased by -2.5% from 1969 to 1978 (95% CI: -3.4% -1.5%) and 0.9% from 1978 to 2007 (95% CI: -1.1% -0.8%), there has been no significant change in brain and other CNS tumor morality in children and adolescents since 2007.
- Although leukemia has historically been the most significant contributor to cancer death in children and adolescents, this trend now means that brain and other CNS tumors are the greatest source of cancer death in this age group.
- Only the youngest age group has continued to make improvements in mortality rates due to brain and other

CNS tumors. In children 0–4 years old, mortality has decreased 1.4% per year from 1969–2018 (95% Cl: -1.6% – -1.3%). Mortality remains stable in all older childhood and adolescent age groups.

## Age-, Sex-, Race-, and Ethnicity-Specific Relative Survival

Five-year relative survival estimates for primary malignant and non-malignant brain and other CNS tumors in the United States during 2001–2017 overall, by sex, race, Hispanic ethnicity and age groups are shown in Table 1.

- Five-year relative survival was higher in females (85.1%) as compared to males (82.8%). When stratified by behavior, five-year survival estimates did not differ by sex for malignant tumors only.
- Adolescents ages 15–19 years had the highest five-year relative survival of any age group (90.5%).
- For malignant tumors only, survival was lowest in infants < 1 year old (60.3%), and highest in children and adolescents ages 10–14 (80.1%) and 15–19 years (79.3%).</li>
- Five-year relative survival was highest in White children and adolescents (84.6%), and lowest in Black children and adolescents (79.1%). When stratified by behavior, this was also true in malignant tumors only (76.8% as compared to 68.3%).
- Non-Hispanic children and adolescents had higher fiveyear relative survival (84.4%) as compared to Hispanic children and adolescents (82.1%). When stratified by behavior, this was also true in malignant tumors only (76.5% as compared to 71.7%).

### Age-, Site-, and Histopathology-Specific Relative Survival

Relative survival estimates for brain and other CNS tumors by histopathology and age at diagnosis are shown in Table 8.

- Overall, one-year survival for all primary brain and other CNS tumors in children and adolescents was 92.5%, this declined to 83.9% for five-year survival, and 81.1% for ten-year survival.
- There was large variation in survival estimates depending upon tumor histopathology; five-year survival rates were 96.8% for pilocytic astrocytoma but are 33.3% for ATRT and 33.6% for high grade glioma.
- Relative survival in high grade glioma was 64.7% one year after diagnosis, but declined to 33.6% five years after diagnosis, and 30.5% at 10 years after diagnosis.
- For embryonal tumors, one-year relative survival was 82.3% but declined to 63.5% five years after diagnosis, and 58.1% at 10 years after diagnosis.
- For pilocytic astrocytoma, survival was high across all estimates: one-year relative survival was 98.8%, while five- and ten-year relative survival was 96.8% and 95.4%, respectively.
- Within each histopathology, relative survival estimates vary substantially by age group.



Abbreviations: CBTRUS, Central Brain Tumor Registry of the United States; NPCR, National Program of Cancer Registries; SEER, Surveillance, Epidemiology and End Results Program.

Fig. 9 Annual Age-Specific Incidence Rates and Annual Percent Change (APC) with 95% Confidence Intervals (95% CI) of Selected Primary Malignant and Non-Malignant Brain and Other Central Nervous System Tumors and Incidence Trends by the Five Most Common Histopathologies by Age Group in All (Ages 0–19 Years), Infants (0–3 Years), Children (Ages 4–14 Years), and Adolescents (Ages 15–19 Years), CBTRUS Childhood and Adolescent Report: US Cancer Statistics—NPCR and SEER, 2004–2018.



Fig. 10 Average Annual Age-Specific Mortality Rates for Malignant Primary Brain and Other Central Nervous System Tumors in Children and Adolescents Ages 0–19 Years by Central Cancer Registry, CBTRUS Childhood and Adolescent Report: NVSS, 2014–2018.





Relative survival estimates for brain and other CNS tumors by site and age are shown in Table 9.

• The highest five-year survival was for tumors occurring in the cranial nerves (98.3%).



**Fig. 12** Annual Age-Specific Mortality Rates of Primary Malignant and Non-Malignant Brain and Other Central Nervous System Tumors and Mortality Trends in Children and Adolescents Ages 0–19 Years by Age Group, CBTRUS Childhood and Adolescent Report: NVSS, 1969–2018.

- The lowest five-year survival was for tumors of the brain stem (58.2%).
- Within each site, relative survival estimates vary substantially by age group.

 Table 8.
 One-, Five-, and Ten-Year Relative Survival Rates<sup>a,b</sup> for Selected Malignant<sup>c</sup> and Non-Malignant<sup>d</sup> Brain and Other Central Nervous System

 Tumors Ages 0–19 Years by Age Groups and Histopathology, NPCR, 2001–2017 (varying)

Histopathology	Age Group	Total Cases (2001–2017)	1-year RS (95% CI)	5-year RS (95% Cl)	10-year RS (95% Cl)
Gliomas	0–19 years	31,698	90.7 (90.4–91.0)	80.0 (79.5–80.5)	77.2 (76.6–77.7)
	<1 year	1,344	88.8 (86.9–90.4)	78.6 (76.1–80.8)	73.1 (70.2–75.7)
	1–4 years	7,919	92.1 (91.5–92.7)	83.1 (82.2–83.9)	80.2 (79.2–81.2)
	5–9 years	8,481	85.6 (84.8–86.3)	74.6 (73.7–75.6)	72.5 (71.5–73.6)
	10–14 years	7,496	92.5 (91.9–93.1)	82.0 (81.1–82.9)	79.9 (78.8–80.9)
	15–19 years	6,458	94.1 (93.5–94.6)	81.2 (80.1–82.2)	77.2 (76.0–78.4)
Pilocytic astrocytoma	0–19 years	10,532	98.8 (98.6–99.0)	96.8 (96.4–97.1)	95.4 (94.9–95.9)
	<1 year	301	93.0 (89.2–95.5)	78.0 (72.4–82.7)	70.0 (63.3–75.6)
	1–4 years	2,793	99.0 (98.5–99.3)	97.4 (96.6–97.9)	95.8 (94.8–96.7)
	5–9 years	2,971	99.0 (98.6–99.3)	97.5 (96.8–98.1)	96.4 (95.5–97.1)
	10–14 years	2,626	98.9 (98.4–99.2)	97.7 (96.9–98.2)	96.5 (95.4–97.3)
	15–19 years	1,841	99.2 (98.6–99.5)	96.6 (95.6–97.5)	95.9 (94.6–96.9)
Other Low grade glioma	0–19 years	6,459	96.6 (96.2–97.1)	89.7 (88.9–90.5)	86.4 (85.4–87.4)
	<1 year	367	94.7 (91.6–96.7)	89.2 (85.1–92.2)	86.8 (82.2–90.3)
	1–4 years	1,117	96.6 (95.4–97.5)	91.8 (90.0–93.4)	90.4 (88.3–92.2)
	5–9 years	1,358	95.8 (94.6–96.8)	89.0 (87.1–90.6)	86.2 (83.9–88.1)
	10–14 years	1,706	96.6 (95.6–97.4)	90.1 (88.5–91.5)	87.9 (86.0–89.6)
	15–19 years	1,911	97.6 (96.8–98.2)	88.7 (87.0–90.2)	82.8 (80.6-84.8)
High grade glioma	0–19 years	6,551	64.7 (63.5–65.9)	33.6 (32.4–34.8)	30.5 (29.3–31.8)
	<1 year	237	71.2 (64.8–76.6)	64.1 (57.3–70.1)	61.6 (54.5–68.0)
	1–4 years	1,245	62.6 (59.8–65.2)	34.0 (31.3–36.8)	31.1 (28.3–34.0)
	5–9 years	2,189	52.0 (49.9–54.1)	23.5 (21.6–25.4)	21.7 (19.8–23.6)
	10–14 years	1,548	71.9 (69.6–74.1)	38.8 (36.2–41.4)	36.0 (33.3–38.6)
	15–19 years	1,332	78.2 (75.8–80.3)	38.3 (35.5–41.2)	32.4 (29.5–35.4)
Other glioma	0–19 years	18,688	97.9 (97.7–98.1)	93.0 (92.5–93.3)	90.3 (89.8–90.8)
	<1 year	740	91.5 (89.1–93.4)	78.0 (74.6–81.1)	70.1 (66.0–73.9)
	1–4 years	5,557	97.9 (97.5–98.3)	92.5 (91.7–93.2)	89.2 (88.2–90.2)
	5–9 years	4,934	97.8 (97.4–98.2)	93.5 (92.7–94.2)	91.4 (90.5–92.3)
	10–14 years	4,242	98.4 (98.0–98.8)	94.5 (93.7–95.2)	92.6 (91.5–93.5)
	15–19 years	3,215	98.6 (98.1–99.0)	94.4 (93.4–95.2)	92.3 (91.0–93.3)
Choroid plexus tumors	0–19 years	1,037	95.5 (94.0–96.6)	89.2 (86.9–91.1)	86.1 (83.4–88.5)
	<1 year	321	92.8 (89.2–95.3)	87.1 (82.5–90.6)	85.0 (79.6–89.0)
	1–4 years	343	94.9 (91.9–96.8)	85.9 (81.3–89.4)	83.4 (78.4–87.3)
	5–9 years	126	96.8 (91.6–98.8)	90.0 (82.5–94.4)	85.4 (76.0–91.3)
	10–14 years	128	99.2 (94.3–99.9)	93.7 (87.1–97.0)	91.5 (81.9–96.1)
	15–19 years	119	99.2 (93.6–99.9)	98.3 (92.8–99.6)	91.8 (81.0–96.6)
Neuronal and mixed neuronal-	0–19 years	2,818	98.6 (98.0–99.0)	95.5 (94.6–96.3)	94.3 (93.2–95.3)
glial tumors	<1 year	79	91.3 (81.9–96.0)	87.0 (76.6–93.0)	87.0 (76.6–93.0)
	1–4 years	367	98.1 (95.9–99.1)	94.4 (91.1–96.6)	93.4 (89.6–95.8)
	5–9 years	524	98.2 (96.6–99.1)	93.3 (90.5–95.3)	92.3 (89.2–94.5)
	10–14 years	873	99.2 (98.3–99.6)	96.7 (95.0–97.8)	95.9 (93.9–97.3)
	15–19 years	975	99.0 (98.0–99.5)	96.8 (95.2–97.9)	94.9 (92.6–96.5)

Table 8.         Continued					
Histopathology	Age Group	Total Cases (2001–2017)	1-year RS (95% Cl)	5-year RS (95% Cl)	10-year RS (95% Cl)
Tumors of the pineal region	0–19 years	550	89.4 (86.5–91.8)	69.9 (65.5–73.9)	62.8 (57.8–67.3)
	<1 year	<50 case	s		
	1–4 years	126	77.4 (69.0–83.8)	50.5 (41.0–59.3)	49.3 (39.7–58.2)
	5–9 years	131	96.8 (91.7–98.8)	74.2 (64.4–81.6)	66.4 (55.7–75.0)
	10–14 years	118	98.3 (93.2–99.6)	83.6 (74.9–89.5)	69.5 (57.6–78.7)
	15–19 years	145	94.4 (89.0–97.2)	78.8 (70.2–85.2)	71.3 (60.9–79.3)
Embryonal tumors	0–19 years	7,397	82.3 (81.4–83.1)	63.5 (62.3–64.7)	58.1 (56.8–59.4)
	<1 year	846	54.9 (51.4–58.2)	41.6 (38.2–45.1)	39.1 (35.6–42.6)
	1–4 years	2,581	74.6 (72.9–76.3)	55.0 (53.0–57.0)	51.7 (49.5–53.8)
	5–9 years	2,124	92.7 (91.5–93.7)	73.5 (71.4–75.5)	67.7 (65.3–69.9)
	10–14 years	1,154	94.3 (92.8–95.5)	74.6 (71.8–77.3)	66.9 (63.5–70.0)
	15–19 years	692	92.6 (90.4–94.4)	72.9 (69.1–76.3)	61.7 (57.2–65.8)
Medulloblastoma	0–19 years	4,747	90.3 (89.4–91.1)	73.6 (72.2–74.9)	67.3 (65.7–68.8)
	<1 year	160	66.9 (58.9–73.7)	56.6 (48.3–64.1)	53.3 (44.7–61.2)
	1–4 years	1,393	82.6 (80.5-84.6)	64.2 (61.5–66.8)	60.4 (57.5–63.2)
	5–9 years	1,750	94.3 (93.1–95.3)	76.4 (74.2–78.5)	70.2 (67.6–72.7)
	10–14 years	915	96.2 (94.7–97.2)	80.8 (77.8–83.5)	73.6 (69.9–77.0)
	15–19 years	529	94.4 (92.0–96.1)	81.4 (77.4–84.7)	69.4 (64.2–74.0)
ATRT	0–19 years	1,000	53.2 (50.0–56.3)	33.3 (30.1–36.4)	30.9 (27.7–34.1)
	<1 year	372	39.0 (33.9–44.0)	19.6 (15.5–24.0)	16.7 (12.6–21.3)
	1–4 years	520	58.4 (54.0–62.6)	39.3 (34.7–43.7)	37.2 (32.6–41.9)
	5–9 years	67	75.2 (62.7–84.0)	55.4 (41.2–67.6)	55.4 (41.2–67.6)
	10–14 years	<50 case	s		
	15–19 years	<50 case	s		
Other embryonal tumors	0–19 years	487	80.7 (76.8–84.0)	67.1 (62.5–71.3)	64.0 (59.1–68.4)
	<1 year	194	80.6 (74.1–85.6)	75.5 (68.5–81.1)	73.9 (66.6–79.8)
	1–4 years	195	77.5 (70.8–82.8)	61.5 (53.9–68.3)	57.7 (49.6–64.9)
	5–9 years	58	85.6 (73.2–92.5)	57.6 (43.0–69.8)	55.5 (40.8–67.9)
	10–14 years	<50 case	s		
	15–19 years	<50 case	s		
Tumors of cranial and spinal	0–19 years	3,120	99.7 (99.4–99.9)	98.6 (98.1–99.0)	97.4 (96.4–98.0)
nerves	<1 year	184	100.0 (**-**)	97.8 (92.6–99.3)	96.8 (91.0–98.9)
	1–4 years	651	100.0 (**-**)	99.2 (98.0–99.7)	98.9 (96.9–99.6)
	5–9 years	650	99.7 (98.7–99.9)	99.0 (97.7–99.6)	97.8 (95.8–98.8)
	10–14 years	659	99.4 (98.3–99.8)	98.0 (96.4–98.9)	97.3 (95.2–98.5)
	15–19 years	976	99.6 (98.9–99.9)	98.6 (97.3–99.2)	96.0 (93.5–97.5)
Tumors of meninges	0–19 years	3,078	97.2 (96.5–97.7)	93.7 (92.6–94.5)	90.6 (89.1–91.9)
	<1 year	369	95.1 (92.1–97.0)	92.0 (88.3–94.6)	91.1 (86.7–94.1)
	1–4 years	402	95.1 (92.4–96.8)	91.0 (87.4–93.6)	87.2 (82.3–90.8)
	5–9 years	377	96.7 (94.3–98.1)	92.4 (88.9–94.8)	87.8 (82.4–91.6)
	10–14 years	651	97.9 (96.4–98.8)	94.5 (92.2–96.1)	91.5 (88.4–93.8)
	15–19 years	1,279	98.2 (97.3–98.8)	94.9 (93.3–96.1)	91.9 (89.5–93.7)
Lymphomas and hematopoietic	0–19 years	288	88.6 (84.3–91.8)	81.6 (76.2–85.8)	78.3 (72.2–83.2)
neoplasms	<1 year	<50 case	s		
	1–4 years	<50 case	s		
	5–9 years	69	94.1 (85.0–97.7)	92.3 (82.4–96.8)	92.3 (82.4–96.8)
	10–14 years	70	92.6 (83.0–96.8)	80.0 (67.2-88.3)	76.0 (60.2-86.2)
	15–19 years	106	83.7 (75.1–89.6)	74.9 (64.9–82.4)	73.5 (63.1–81.3)

# Neuro-Oncology

Table 8.         Continued					
Histopathology	Age Group	Total Cases (2001–2017)	1-year RS (95% Cl)	5-year RS (95% CI)	10-year RS (95% CI)
Germ cell tumors	0–19 years	2,274	93.7 (92.6–94.7)	88.6 (87.2–90.0)	85.7 (83.9–87.3)
	<1 year	163	65.0 (57.0–72.0)	61.5 (53.3–68.7)	61.5 (53.3–68.7)
	1–4 years	101	89.7 (81.7–94.3)	83.6 (74.1–89.8)	80.5 (68.8–88.2)
	5–9 years	379	95.9 (93.3–97.5)	92.3 (88.8–94.7)	87.2 (82.0–90.9)
	10–14 years	869	97.1 (95.8–98.1)	91.2 (88.9–93.1)	87.8 (84.8–90.2)
	15–19 years	762	95.5 (93.7–96.7)	90.4 (87.9–92.4)	88.2 (85.3–90.6)
Tumors of the pituitary	0–19 years	7,495	99.9 (99.8–100.0)	99.8 (99.5–99.9)	99.4 (98.9–99.6)
	<1 year	<50 cas	es		
	1–4 years	80	98.7 (90.9–99.8)	97.2 (89.1–99.3)	94.8 (83.7–98.4)
	5–9 years	552	100.0 (**-**)	100.0 (**-**)	100.0 (**-**)
	10–14 years	1,501	99.9 (99.3–100.0)	99.6 (98.9–99.9)	99.2 (98.1–99.7)
	15–19 years	5,336	99.9 (99.7–100.0)	99.9 (99.7–100.0)	99.5 (98.8–99.8)
Craniopharyngioma	0–19 years	2,099	98.5 (97.9–98.9)	95.4 (94.3–96.3)	92.2 (90.6–93.6)
	<1 year	<50 cas	es		
	1–4 years	353	98.9 (96.9–99.6)	95.1 (91.8–97.1)	92.1 (87.5–95.1)
	5–9 years	743	98.5 (97.3–99.2)	96.0 (94.1–97.3)	93.1 (90.3–95.1)
	10–14 years	566	99.1 (97.8–99.6)	96.4 (94.2–97.8)	93.0 (89.6–95.3)
	15–19 years	411	98.0 (96.0–99.0)	94.0 (90.8–96.1)	91.2 (86.7–94.2)
Other/unclassified tumors	0–19 years	3,371	92.5 (91.6–93.4)	89.8 (88.7–90.9)	88.8 (87.5–90.0)
	<1 year	257	70.1 (63.9–75.4)	67.8 (61.6–73.3)	67.8 (61.6–73.3)
	1–4 years	562	88.1 (85.1–90.6)	83.9 (80.4–86.8)	83.2 (79.7–86.2)
	5–9 years	596	92.5 (90.0–94.4)	89.6 (86.7–91.9)	86.7 (82.9–89.7)
	10–14 years	858	95.3 (93.6–96.5)	92.3 (90.2–94.0)	91.8 (89.4–93.6)
	15–19 years	1,098	98.0 (96.9–98.7)	96.2 (94.7–97.3)	95.3 (93.3–96.7)
Total <sup>e</sup>	0–19 years	65,402	92.5 (92.2–92.7)	83.9 (83.6–84.2)	81.1 (80.7–81.4)
	<1 year	3,639	80.3 (79.0–81.6)	71.9 (70.3–73.4)	68.6 (66.9–70.2)
	1–4 years	13,562	89.4 (88.9–89.9)	79.3 (78.5–80.0)	76.5 (75.7–77.3)
	5–9 years	14,774	90.0 (89.5–90.5)	79.9 (79.2–80.6)	77.1 (76.3–77.9)
	10–14 years	14,997	95.1 (94.7–95.5)	87.0 (86.4–87.6)	84.5 (83.8–85.1)
	15–19 years	18,430	96.9 (96.7–97.2)	90.5 (90.0–90.9)	87.5 (86.9–88.1)

<sup>a</sup>The cohort analysis of survival rates was utilized for calculating the survival estimates presented in this table. Long-term cohort-based survival estimates reflect the survival experience of individuals diagnosed over the time period, and they may not necessarily reflect the long-term survival outlook of newly diagnosed cases.

<sup>b</sup>Rates are an estimate of the percentage of patients alive at one, two, three, four, five, and ten year, respectively.

<sup>c</sup>Assigned behavior code of/3 by the International Classification for Disease, Oncology 3<sup>rd</sup> edition (see Supplementary Table 3).

<sup>d</sup>Assigned behavior code of/0 or/1 by the International Classification for Disease, Oncology 3<sup>rd</sup> edition (see Supplementary Table 3). <sup>e</sup>Includes histopathologies not listed in this table.

Data are not presented when fewer than 50 cases were reported for the specific category or where less than 16 individuals remain alive at the end of the observation period.

\*\*Not able to be calculated.

Abbreviations: NPCR, National Program of Cancer Registries; RS, Relative Survival; ATRT, Atypical teratoid/rhabdoid tumor.

Relative survival estimates for high grade glioma of the brain stem are shown in Table 4.

- One-year survival after diagnosis with these tumors was 61.5%, while 15-year survival was 35.1%.
- Five-year survival is highest in children diagnosed at < 1 year (75.8%) and lowest in children diagnosed at ages 5–9 years (25.1%).

### Trends in Survival

Kaplan-Meier survival curves were generated for all high-grade gliomas (Figure 13A) and medulloblastoma (Figure 13B) in individuals 0–19 years of age, using a log rank test to evaluate differences. There were 5,364 high-grade glioma patients and 3,698 medulloblastoma assessed. Although increased survival in high-grade glioma

 Table 9.
 One-, Five-, and Ten-Year Relative Survival Rates<sup>a,b</sup> for Selected Malignant<sup>c</sup> and Non-Malignant<sup>d</sup> Brain and Other Central Nervous System

 Tumors Sites Ages 0–19 Years by Age Groups and Site, NPCR, 2001–2017 (varying)

Site	Age Group	Total Cases (2001–2017)	1-year RS (95% CI)	5-year RS (95% CI)	10-year RS (95% CI)
Frontal lobe	0–19 years	3,753	93.5 (92.6–94.2)	81.6 (80.2–82.9)	77.3 (75.6–78.8)
	0 years	127	75.7 (66.9–82.4)	69.1 (59.7–76.7)	69.1 (59.7–76.7)
	1–4 years	584	87.1 (84.1–89.6)	75.8 (71.9–79.2)	72.3 (68.0–76.2)
	5–9 years	659	94.2 (92.1–95.8)	83.3 (80.0–86.1)	79.3 (75.4–82.6)
	10–14 years	1,002	94.9 (93.3–96.2)	84.9 (82.3–87.2)	82.4 (79.4–85.0)
	15–19 years	1,381	96.3 (95.1–97.2)	81.9 (79.5–84.0)	75.4 (72.4–78.1)
Temporal lobe	0–19 years	4,339	96.5 (95.9–97.0)	89.5 (88.5–90.5)	86.3 (85.0–87.5)
	0 years	159	93.5 (88.0–96.5)	88.5 (81.9–92.8)	87.6 (80.7–92.1)
	1–4 years	646	94.4 (92.3–96.0)	90.6 (87.9–92.7)	87.4 (83.9–90.2)
	5–9 years	842	96.0 (94.4–97.1)	88.0 (85.4–90.1)	84.9 (81.8–87.5)
	10–14 years	1,225	96.4 (95.1–97.3)	90.0 (88.0–91.6)	87.0 (84.5–89.2)
	15–19 years	1,467	98.1 (97.2–98.7)	89.8 (87.9–91.4)	85.8 (83.4–87.8)
Parietal lobe	0–19 years	1,847	92.8 (91.5–93.9)	80.6 (78.5-82.4)	76.6 (74.2–78.7)
	0 years	76	77.9 (66.6–85.8)	70.3 (58.1–79.5)	67.9 (55.1–77.7)
	1–4 years	326	89.0 (85.0–92.0)	77.1 (71.9–81.6)	76.0 (70.6–80.6)
	5–9 years	346	94.0 (90.9–96.1)	80.9 (75.9–84.9)	78.5 (73.1–82.9)
	10–14 years	519	94.7 (92.3–96.3)	84.1 (80.3–87.1)	80.6 (76.3–84.2)
	15–19 years	580	94.4 (92.2–96.0)	80.6 (76.9-83.8)	73.3 (68.5–77.4)
Occipital lobe	0–19 years	765	96.4 (94.8–97.5)	88.7 (86.0–90.9)	85.1 (81.8–87.9)
·	, 0 vears	<50 cases			
	1–4 vears	106	92.2 (85.0–96.0)	82.3 (73.0–88.7)	77.5 (66.7–85.1)
	5–9 vears	142	97.1 (92.5–98.9)	91.1 (84.4–95.0)	89.0 (81.5–93.5)
	10–14 vears	228	98.6 (95.8–99.6)	90.0 (84.6–93.5)	88.4 (82.4–92.4)
	15–19 years	251	96.8 (93.6–98.4)	89.3 (84.2–92.8)	83.8 (77.0-88.8)
Cerebrum	0–19 vears	3.599	87.5 (86.4–88.6)	71.4 (69.8–72.9)	68.3 (66.6–70.0)
Concertain	0 vears	216	74.9 (68.4–80.2)	64.9 (57.8-71.1)	61.7 (54.2–68.3)
	1–4 vears	739	89.0 (86.4–91.1)	78 4 (75 1-81 4)	74.9 (71.1–78.3)
	5–9 vears	945	85.6 (83.2–87.8)	70.7 (67.5–73.6)	66.7 (63.2–70.0)
	10–14 vears	980	90.2 (88.1–91.9)	70.9 (67.7–73.8)	69.0 (65.7–72.1)
	15–19 vears	719	88.6 (86.0–90.8)	67.7 (63.9–71.2)	64.7 (60.5–68.5)
Ventricle	0–19 years	3.446	92.9 (91.9–93.7)	86.1 (84.9–87.3)	82.5 (81.0-84.0)
	0 vears	521	86.2 (82.8-89.0)	80.9 (77.0-84.2)	79.2 (74.9–82.8)
	1–4 vears	861	89 5 (872–914)	79 9 (76 9–82 6)	73.8 (70.2–771)
	5-9 years	639	94 5 (92 4-96 1)	873 (84 3-89 8)	83 3 (79 5-86 4)
	10–14 years	740	96.8 (95.2–979)	91 3 (88 9-93 3)	89 2 (86 2-91 6)
	15–19 years	685	96 3 (94 5-975)	91 2 (88 6–93 2)	88.0 (84.6-90.6)
Cerebellum		9 201	93 5 (93 0-94 0)	83.6 (82.8-84.4)	80.3 (79.4_81.2)
Cerebendin	0 vears	333	62 3 (56 8_67 <i>4</i> )	A78 (A2 1_53 3)	45 2 (39 3_50 9)
		2 522	89.7 (88.4-00.8)	78 6 (76 8 - 80 2)	45.2 (33.3-50.3)
	5-9 years	2,332	96.2 (95.4-96.8)	76.0 (70.0-80.2) 85.3 (83.8-86.7)	82.0 (80.2 83.5)
	10-14 years	2,818	90.2 (95.4-90.8)	80.3 (877-90.7)	86.0 (84.1-877)
	15_10 vooro	1,507	97.2 (90.4-97.3)	89.4 (875-00.0)	85 3 (82 0 872)
Proin stom	15–19 years	7500	37.2 (30.2-37.3)	69.4 (67.5-90.9)	65.3 (62.9-67.3)
DI AITI SLEITI		1,022	70.9 (70.4 01.0)	50.2 (37.0 - 33.4)	50.2 (54.0-50.5)
	u years	203	70.2 (70.4-81.0)	03.4 (30.9-09.3)	55.0 (52.0-55.4)
	I-4 years	2,001	/σ.υ (/4. I=/ /.δ)	54.8 (52.5-57.U)	51.8 (49.4-54.2)
	5-9 years	2,020	00.U (04.1-07.8)	40.0 (44.0-48.0)	44.4 (42.3-40.4)
	10-14 years	1,000	04.1 (02.1-05.0)	00.3 (00.4-7 1.3)	00.0 (02.3-08.2)
	io-io years	1,002	03.2 (07.1-91.0)	//./ (/4.0-80.3)	/3./(/0.4–/0./)

Table 9.   Continued					
Site	Age Group	Total Cases (2001–2017)	1-year RS (95% CI)	5-year RS (95% CI)	10-year RS (95% Cl)
Spinal cord and	0–19 years	3,326	94.6 (93.8–95.4)	89.1 (87.8–90.2)	86.4 (84.9–87.7)
cauda equina	0 years	390	93.0 (89.8–95.3)	90.4 (86.7–93.2)	90.4 (86.7–93.2)
	1–4 years	660	93.2 (91.0–94.9)	88.0 (85.1–90.4)	86.4 (83.0–89.1)
	5–9 years	546	94.7 (92.4–96.3)	88.4 (85.1–91.0)	84.6 (80.5–87.9)
	10–14 years	790	94.3 (92.4–95.8)	87.9 (85.3–90.2)	84.5 (81.1–87.4)
	15–19 years	940	96.5 (95.1–97.5)	90.6 (88.3–92.4)	87.6 (84.6–90.0)
Cranial nerves	0–19 years	4,444	99.7 (99.5–99.9)	98.3 (97.8–98.7)	97.5 (96.8–98.0)
	0 years	252	99.4 (94.4–99.9)	93.2 (88.6–96.0)	91.3 (86.2–94.6)
	1–4 years	1,709	100.0 (98.8–100.0)	99.2 (98.4–99.6)	98.8 (97.9–99.4)
	5–9 years	1,061	99.7 (99.1–99.9)	98.6 (97.5–99.2)	97.6 (96.0–98.5)
	10–14 years	674	99.7 (98.8–99.9)	98.5 (97.0–99.3)	97.8 (96.0–98.8)
	15–19 years	748	99.4 (98.3–99.7)	97.4 (95.6–98.4)	95.8 (93.0–97.5)
Meninges	0–19 years	1,557	97.3 (96.3–98.0)	93.9 (92.4–95.1)	91.0 (88.9–92.6)
	0 years	76	85.5 (74.9–91.9)	82.3 (71.0–89.5)	79.0 (65.6–87.7)
	1–4 years	155	92.7 (87.2–95.9)	86.5 (79.6–91.3)	81.5 (72.9–87.6)
	5–9 years	189	97.8 (94.3–99.2)	94.0 (89.1–96.8)	91.6 (84.8–95.4)
	10–14 years	356	98.0 (95.8–99.0)	95.2 (92.1–97.2)	91.9 (87.7–94.8)
	15–19 years	781	98.9 (97.8–99.4)	95.9 (93.9–97.2)	93.4 (90.3–95.5)
Pituitary and	0–19 years	9,672	99.7 (99.5–99.8)	99.0 (98.8–99.2)	98.0 (97.5–98.4)
craniopharyngeal duct	0 years	50	96.4 (83.8–99.2)	85.5 (69.1–93.6)	76.9 (57.0–88.5)
	1–4 years	388	98.9 (97.2–99.6)	96.6 (93.9–98.2)	93.6 (89.6–96.1)
	5–9 years	1,256	99.3 (98.7–99.7)	98.3 (97.2–98.9)	96.6 (94.8–97.8)
	10–14 years	2,111	99.7 (99.3–99.9)	98.7 (98.0–99.2)	97.6 (96.4–98.4)
	15–19 years	5,867	99.8 (99.7–99.9)	99.6 (99.3–99.8)	98.9 (98.3–99.3)
Pineal gland	0–19 years	1,832	92.0 (90.7–93.2)	81.9 (79.9–83.7)	78.1 (75.8–80.3)
	0 years	65	54.7 (41.6–66.0)	40.1 (27.6–52.3)	40.1 (27.6–52.3)
	1–4 years	211	79.3 (73.1–84.2)	59.3 (52.0–65.9)	56.6 (48.9–63.6)
	5–9 years	311	94.6 (91.4–96.7)	82.9 (77.6–87.1)	75.4 (68.6–80.9)
	10–14 years	600	97.2 (95.5–98.3)	89.0 (85.9–91.5)	84.9 (80.9–88.1)
	15–19 years	645	94.0 (91.8–95.6)	86.6 (83.5–89.2)	84.1 (80.4–87.1)

<sup>a</sup>The cohort analysis of survival rates was utilized for calculating the survival estimates presented in this table. Long-term cohort-based survival estimates reflect the survival experience of individuals diagnosed over the time period, and they may not necessarily reflect the long-term survival outlook of newly diagnosed cases.

<sup>b</sup>Rates are an estimate of the percentage of patients alive at one, two, three, four, five, and ten year, respectively.

<sup>c</sup>Assigned behavior code of/3 by the International Classification for Disease, Oncology 3<sup>rd</sup> edition (see Supplementary Table 3).

<sup>d</sup>Assigned behavior code of/0 or/1 by the International Classification for Disease, Oncology 3<sup>rd</sup> edition (see Supplementary Table 3).

Abbreviations: NPCR, National Program of Cancer Registries; RS, Relative Survival.

is observed in 2013–2017 compared to 2004–2007, the improvement is not statistically significant (log rank p = 0.16). Similarly, there was a trend towards increased survival for 2013–2017 among medulloblastoma patients, though not statistically significant (log rank p = 0.051).

Age-stratified multivariable Cox proportional hazard models, adjusted for sex, race/ethnicity, and treatment pattern, were generated to assess survival differences by time period of diagnosis. The use of surgery and/or radiation was utilized for the determination of treatment patterns. HR decreased for high grade glioma and medulloblastomas for each time period when compared to 2004–2007 (Figure 14). Significant improvement in survival was observed for patients diagnosed with medulloblastomas in 2013–2017 compared to 2004–2007 (HR = 0.79; 95% Cl = 0.65-0.96; p = 0.002).

### Age-specific and Histopathology-Specific Annual Case Projections

The estimated number of cases of all primary brain and other CNS tumors for 2023, 2024, and 2025 are shown by



Fig. 13 Survival by Year of Diagnosis in Children and Adolescents Ages 0–19 Years for A) High Grade Gliomas and B) Medulloblastoma, CBTRUS Childhood and Adolescent Report: US Cancer Statistics—NPCR, 2004–2018.

histopathology and age group in Table 10. Estimated numbers of cases are highly dependent on input data. Different patterns of incidence within strata can substantively affect the projected estimates, and strata-specific estimates may not equal the total estimate presented. **Caution should be used when utilizing these estimates**.

- The total number of new cases of primary brain and other CNS tumors projected to occur in children and adolescents ages 0–19 years in 2023 was 5,260.
- The greatest number of new cases was estimated to be in adolescents ages 15–19 years, in which 1,660 newly diagnosed cases are expected in 2023.
- Pilocytic astrocytoma had the highest number of estimated new cases, with 860 new cases expected to be diagnosed in 2023.
- The histopathology with the second largest number of estimated new cases was tumors of the pituitary, with 800 cases estimated to be diagnosed in 2023, the majority of which will be in adolescents ages 15–19 years.

### Comparing Brain and Other CNS Tumors to Other Common Child and Adolescent Cancers

Average annual age-specific incidence rates for the top five most common cancers in children and adolescents overall and by age groups are shown in Figure 15.

• The most common cancer overall in children ages 0–19 years was primary brain and other CNS tumors. Brain and other CNS tumors were the most common cause of cancer in all age groups other than ages 1–4 years, where leukemia was the most common cause of cancer.



Fig. 14 Hazard Ratios and 95% Confidence Intervals by Year of Diagnosis for Death Due to High Grade Glioma and Medulloblastoma in Children and Adolescents Ages 0–19 Years, Adjusted for Sex, Race/Ethnicity, and Treatment, CBTRUS Childhood and Adolescent Report: US Cancer Statistics—NPCR, 2004–2017.

Average annual age-specific mortality rates for the top five most common causes of death and top five most common causes of cancer death in children and adolescents overall and by age groups are shown in Figure 16.

• The most common cancer death in children ages 0–19 years was primary brain and other CNS tumors. Brain and other CNS tumors were the most common cause of cancer death in children ages 5–14 years, while among children ages 0–4 and 15–19 years, leukemia was the most common cause of cancer death.

### Prevalence of Brain and CNS tumors and Other Common Child and Adolescent Cancers

Estimates of the number of prevalent cases of cancer among children ages 0–19 years in the United States in 2022 are shown in Figure 17 and Table 11.

- There were 40,594 prevalent brain tumor cases in children and adolescents ages 0–19 years in 2022. The most prevalent type of cancer overall was leukemia, which was estimated to have 40,738 prevalent cases.
- 22,527 of these brain tumor cases are estimated to be in children 0–14 years old, while there were estimated to be 18,067 prevalent cases in adolescents 15–19 years old.
- The histopathologic group with the highest prevalence was gliomas, with 18,334 cases.
- The next most prevalent histopathologic groups were embryonal tumors (4,230 cases) and tumors of the sellar region (4,589 cases).

		חופארפוור וו													
Histopathology	2023					2024					2025				
	0–19	4-0	5-9	10-14	15-19	0–19	0-4	5-9	10–14	15–19	0–19	0-4	59	10–14	15–19
	years	years	years	years	years	years	years	years	years	years	years	years	years	years	years
Gliomas <sup>c</sup>	2,160	590	610	560	460	2,160	590	620	560	460	2,170	600	620	560	470
Pilocytic astrocytoma	860	290	250	200	140	870	290	250	200	140	870	290	250	200	140
Other Low grade glioma	440	100	06	130	130	440	100	06	130	130	440	100	06	130	130
High grade glioma	410	70	160	130	110	410	70	160	130	110	410	70	160	130	110
Other glioma	440	130	120	100	80	440	130	120	100	80	440	130	120	100	80
Ependymal tumors	250	100	50	50	50	250	100	50	50	50	250	100	50	50	50
Choroid plexus tumors	80	50	I	I	ł	80	50	1	ł	1	80	50	I	I	I
Neuronal and mixed neuronal- glial tumors	270	40	50	06	100	270	40	50	06	100	270	40	50	06	100
Tumors of the pineal region	40	I	1	1	1	40	1	1	I	I	40	1	I	1	1
Embryonal tumors	490	210	140	80	40	490	210	140	80	40	490	210	140	80	40
Medulloblastoma	340	110	120	70	30	340	110	120	70	30	340	110	120	70	30
ATRT	06	80	ł	1	1	90	80	I	I	1	06	80	I	ł	ł
Other embryonal tumors	60	20	ł	1	ł	60	20	I	1	1	60	20	I	ł	ł
Tumors of cranial and spinal nerves	240	50	40	60	06	240	50	40	60	06	240	50	40	60	06
Tumors of meninges	270	60	40	60	110	270	60	40	60	110	270	60	40	60	110
Lymphomas and hematopoietic neoplasms	30	ł	ł	I	I	30	I	ł	I	I	30	I	1	I	I
Germ cell tumors	180	20	30	70	60	180	20	30	70	60	180	20	30	70	60
Tumors of sellar region	960	40	140	210	590	960	40	140	210	590	960	40	140	210	590
Tumors of the pituitary	800	I	ł	160	550	800	ł	I	160	550	800	ł	I	160	550
Craniopharyngioma	170	I	I	50	30	170	ł	ł	50	30	170	1	I	50	30
Other/unclassified tumors	300	80	70	06	06	300	80	70	06	06	300	80	70	06	06
Total <sup>d</sup>	5,260	1,220	1,180	1,290	1,660	5,260	1,220	1,180	1,290	1,660	5,260	1,220	1,180	1,290	1,660
*Source: Estimation based on CBTRU <sup>b</sup> Rounded to the nearest 10. Numbers <sup>c</sup> CBTRUS defines the broad category <sup>d</sup> Includes histopathologies not listed <sup>d</sup> Includes not presented when fewer <b>Abbreviations</b> : CBTRIIS, Central Br	S NPCR a s may not of glioma in this tab than 16 c	nd SEER 20 add up due s to includu le. ases were	000–2018 da to roundin; 9 ICD-0-3 h estimated f	ita for malign g. istopatholog or the specif	lant tumors, i y codes 9380 iic category.	-9384, 9391 -9384, 9391 These case	and SEER 20 	)06–2018 da ). ded in over	ita for non-m all rates. FR Surveills	nalignant tum ance Fnidem	lors. iology and	End Results	s Program: A	TRT Atvnic	al teratoid/

rhabdoid tumor.



Fig. 15 Average Annual Age-Specific Incidence Rates with 95% Confidence Intervals and Average Annual Cases for All Primary Malignant and Non-Malignant Brain and Other Central Nervous System Tumors Ages 0–19 Years in Comparison to Top Five Highest Incidence Cancers for Children and Adolescents Overall and by Age Groups, CBTRUS Childhood and Adolescent Report: US Cancer Statistics—NPCR and SEER, 2014–2018.

• As these estimates include only children and adolescents 0–19 years of age at time of prevalence estimate, the total population of childhood and adolescent brain tumor survivors including those that are now in adulthood is significantly larger.

### Risk Factors, Long Term, and Late Effects for Childhood and Adolescent Brain and CNS Tumors

Despite being the greatest contributor to cancer mortality in children and adolescents ages 0–19 years, little is known about the etiology of childhood brain and other CNS tumors. There are a few established risk factors for brain and other CNS tumors in children and adolescents, including single gene inherited disorders, genetic syndromes, and ionizing radiation.<sup>32,33</sup>

Genetic risk factors for child and adolescent brain and CNS tumors— As compared to adults, there have been minimal germline genetic studies conducted in children and adolescents with brain and other CNS tumors. Approximately 4% of gliomas diagnosed in children and

adolescents are attributable to single-gene Mendelian disorders or inherited genetic cancer syndromes, and ~5–10% of children and adolescents diagnosed with brain and other CNS tumors have a family history.<sup>32,33</sup> The majority of these inherited syndromes are characterized by loss-of-function mutations in tumor suppressor genes.<sup>32,33</sup> A summary of the most commonly occurring syndromes is shown in Supplementary Table 5.

As compared to those in adult brain and other CNS tumors, relatively few candidate gene and genomewide association studies (GWAS) have been conducted to identify more common (occurring in > 1% of the population) genetic variations that can affect risk of childhood and adolescent brain tumors. A summary of identified single nucleotide polymorphism (SNP) associations is shown in SupplementaryTable 6. Similar to prior findings in adult glioma, some implicated genes are involved in processes regulating telomere length (such as regulator of telomere elongation helicase 1 [*RTEL1*] and telomerase reverse transcriptase [*TERT*]).<sup>34</sup> A genetic predisposition to longer telomere length or more efficient maintenance is a suspected risk factor contributing to incidence of childhood neuroblastoma and ependymoma



Fig. 16 Annual Average Age-Specific Mortality Rates with 95% Confidence Intervals and Average Annual Deaths for Primary Malignant Brain and Other CNS Tumors in Ages 0–19 years as Compared to the Top Five Causes of Death and Top Five Caucer Causes of Death for Children and Adolescents, Overall and by Age Groups, CBTRUS Childhood and Adolescent Report: NVSS, 2014–2018.

(statistical significance found only for those  $\ge 12$  years at age of diagnosis).<sup>34,35</sup> GWAS continue to implicate novel genes such as protein-coding gene leucine rich repeat containing 4C (*LRRC4C*, located at 11q12) and metalloproteinase pappalysin 2 (*PAPPA2*, located at 1q25.2) which Foss-Skiftesvik et al. observed as associated with increased risk of childhood CNS tumors.<sup>36</sup> Further large-scale genetic studies utilizing SNP-array and nextgeneration sequencing data are needed to identify and validate common and rare germline variants associated with increased risk of primary brain and other CNS tumors in children and adolescents.

Literature regarding the inheritance of primary brain and other CNS tumors remains inconsistent and limited due to the rarity of cases. Recently, a study evaluated incidence rates and family risk of tumors of the CNS and leukemia among individuals from Norway and individuals with Scandinavian ancestry in a single US state, two settings with high quality multigenerational genealogical and cancer registry records.<sup>37</sup> Kollerud et al. observed a 3-fold increased risk of developing CNS tumors in Utah and Norway among children with a first-degree relative diagnosed with CNS tumors.<sup>37</sup> Another study from France found an increased risk of childhood and adolescent brain tumors with a family history of brain tumor in first- and second-degree relatives.<sup>38</sup> While these findings are consistent with some prior studies, the sample may be influenced by the high representation rates of European genetic-ancestry which have been associated with a higher risk of childhood and adolescent brain and other CNS tumors.<sup>39</sup>

Environmental and Individual Risk Factors for Childhood and Adolescent Brain and Other CNS Tumors— Numerous potential risk factors for brain and other CNS tumors in children have been examined, but the only consistently validated factor known to increase risk of these tumors is exposure to ionizing radiation. Ionizing radiation has carcinogenic effects which are shown to be stronger in children due to their increased radiosensitivity and longer life expectancy.<sup>40</sup> In the United States, the most common man-made radiation exposure to children is from Computed tomography (CT) scan use.<sup>41</sup> Associations between CT scans and increased risk of childhood and adolescent brain and other CNS tumors has been reported by research groups in numerous



Fig. 17 Estimated Prevalent Cases in the United States in 2022 in Children and Adolescents Ages 0–19 Years for A) the Eight Most Prevalent Cancers in Children and Adolescents, B) by the Ten Most Prevalent Brain and Other Central Nervous System Histopathologies CBTRUS Childhood and Adolescent Report: US Cancer Statistics—NPCR and SEER, 1975–2018 (varying).

countries, including the United Kingdom (UK), Australia, Taiwan, Germany, the Netherlands, and France.<sup>42–48</sup>

While it is established that moderate to high doses of ionizing radiation are associated with increased risk of childhood cancers, a recent meta-analysis on low dose exposures of ionizing radiation (such as that from X-ray) suggests that lower levels of ionizing radiation may also cause excess risk for certain types of childhood cancers including brain and other CNS tumors.<sup>41</sup> Additionally, this meta-analysis indicated (although not statistically significant) higher risks of brain and other CNS tumors among those exposed in utero via maternal diagnostic imagery than for postnatal exposure.<sup>41</sup> A 2021 systematic review of risk of childhood cancers associated with cumulative radiation doses from radiological imaging emphasizes the selective use of CT imaging and the continued need for dose-risk monitoring.<sup>49</sup>

Non-ionizing radiation, such as that emitted by cellular phones or extremely low-frequency (ELF) magnetic fields, has been repeatedly evaluated as a risk factor for brain and other CNS tumors in children and adolescents. Particular attention has been paid to radiofrequency (RF) radiation which is emitted from technology such as mobile phones and wireless networks, use of which has become much more common among children and young adults in the last several decades. As of 2011, the IARC has classified RF as a possible carcinogen.<sup>50,51</sup> A review of risk factors by Vienne-Jumeau et al. found evidence supporting an association between RF exposure and acoustic neuroma in long-term users (adults), but report a lack of significant and consistent evidence for a validated associated between RF exposure and childhood brain and other CNS tumors.<sup>50</sup>To date, there is no conclusive evidence that RF or ELF magnetic fields, at the levels emitted by mobile phones may increase the risk brain and other CNS tumors, as reported by Castaño-Vinyals et al. in a large case control study focused on childhood exposures.<sup>52</sup>

Many factors related to birth, such as gestational age, birth weight, and birth defects have been evaluated for potential associations with risk of childhood and adolescent brain tumors.<sup>53</sup> Birth circumstances suspected to be associated with higher risk of developing childhood brain and other CNS tumors include being male, high birth weight (>=4000 g), being born larger for gestational age, and being pre-term (<37 weeks).<sup>32</sup> Various studies and metaanalysis support that high birth weight is associated with an increased risk of childhood brain and other CNS tumors overall, particularly astrocytoma and embryonal tumors. A potential association between instrument-assisted delivery and increased risk of childhood brain and other CNS tumors was recently assessed in multiple large population studies, with inconsistent findings. Recent studies done in the United States, Greece, and Denmark found an increased risk of CNS tumors with instrument-assisted delivery.54,55 The United States and Greece studies found effect estimates for instrument-assisted delivery were stronger for astrocytomas.<sup>54,55</sup> Approximately 7% of childhood brain and other CNS tumors are thought to be attributable to non-chromosomal structural birth defects (not including known single gene syndromes or chromosomal birth defects such as Down's syndrome).<sup>56</sup> The findings of a recent study using 10 million live birth records showed increased odds of CNS tumors given a non-chromosomal birth defect, but also observed a positive risk association between the total number of major non-chromosomal birth defects per child and the risk of cancer (including CNS tumors) with greater risks among children with two or more major birth defects.56

Many other environmental and parental risk factors have been investigated as contributors to childhood brain and other CNS tumor risk, which remain unvalidated or with inconsistent findings. Some of these evaluated factors include advanced parental age, maternal dietary N-nitroso compounds (NOCs) consumption, and pre-and post-natal exposure to pesticides.<sup>32</sup> Currently, studies consistently suggest that children of parents with indicators of lower socioeconomic status (SES) (including lower educational attainment, lower income, and/or participation in public insurance programs) have reduced risk of childhood brain and other CNS tumors.<sup>57</sup> Offspring of parents with higher SES appear to be at increased risk of developing childhood and adolescent brain and other CNS tumors. This finding may be due to a yet unknown environmental exposure associated with higher SES but may also be indicative of broader social concerns such as disproportionate access to quality care, which may create differential rates of diagnosis. A metaanalysis of international trends in incidence of brain tumors in children and young adults observed a significant association between childhood brain tumor incidence and gross domestic product per capita, suggesting a positive relationship between incidence and national economic wealth, where high income countries had higher

 Table 11.
 Estimated Prevalent Case Counts<sup>a</sup> and Crude Prevalence Rate per 100,000 for Brain and Other Central Nervous System Tumors Ages 0–19

 Years Overall, by Histopathology Groupings and Age Groups, 2022, CBTRUS Childhood and Adolescent Report: NPCR and SEER, 1975–2018

Histopathology	0-19Years		0-14Years		15–19 Years	
	Prevalent cases	Crude Preva- lence Rate per 100,000	Prevalent cases	Crude Prevalence Rate per 100,000	Prevalent cases	Crude Preva- lence Rate per 100,000
Gliomas <sup>b</sup>	18,334	23.31	10,644	18.53	7,690	36.28
Pilocytic astrocytoma	8,264	10.51	4,907	8.54	3,357	15.84
Other Low grade glioma	3,750	4.77	1,991	3.47	1,759	8.30
High grade glioma	1,755	2.23	1,011	1.76	743	3.51
Other glioma	4,547	5.78	2,735	4.76	1,812	8.55
Ependymal tumors	2,436	3.10	1,524	2.65	912	4.30
Choroid plexus tu- mors	195	0.25	112	0.19	83	0.39
Neuronal and mixed neuronal-glial tumors	1,259	1.60	608	1.06	651	3.07
Tumors of the pineal region	195	0.25	112	0.19	83	0.39
Embryonal tumors	4,230	5.38	2,701	4.70	1,529	7.21
Medulloblastoma	3,197	4.07	1,936	3.37	1,260	5.95
ATRT	516	0.66	423	0.74	93	0.44
Other embryonal tumors	274	0.35	200	0.35	74	0.35
Tumors of cranial and spinal nerves	2,171	2.76	1,059	1.84	1,112	5.25
Tumors of meninges	1,516	1.93	823	1.43	693	3.27
Lymphomas and he- matopoietic neoplasms	195	0.25	112	0.19	83	0.39
Germ cell tumors	1,259	1.60	608	1.06	651	3.07
Tumors of sellar region	4,589	5.84	1,659	2.89	2,929	13.82
Tumors of the pi- tuitary	3,031	3.85	820	1.43	2,211	10.43
Craniopharyngioma	1,558	1.98	839	1.46	719	3.39
<b>UnclassifiedTumors</b>	2,431	3.09	1,414	2.46	1,018	4.80
Total <sup>c</sup>	40,594	51.58	22,527	39.22	18,067	85.23

<sup>a</sup>Source: Estimation based on CBTRUS NPCR and SEER 2000–2018 data for malignant tumors, and NPCR and SEER 2004–2018 data for non-malignant tumors.

<sup>b</sup>CBTRUS defines the broad category of gliomas to include ICD-0-3 Histopathology codes 9380–9384, 9391–9460, 9480.

<sup>c</sup>Includes histopathologies not listed in this table.

Abbreviations: CBTRUS, Central Brain Tumor Registry of the United States; NPCR, National Program of Cancer Registries; SEER, Surveillance, Epidemiology, and End Results Program; ATRT, Atypical teratoid/rhabdoid tumor.

rates compared to low-middle income countries.<sup>58</sup> The study posits many reasons for these findings including high income countries having larger populations of European ancestry (a factor independently associated with risk of childhood and adolescent brain and other CNS tumors) and higher rates of CT imaging, while low-middle income countries may be underrepresented due to minimal access to diagnostic healthcare services.<sup>58</sup> However, further investigations to identify specific risk factors for each histopathological subtype are required

due to the potentially diverse etiologies of these heterogenous malignancies.

Long-Term and Late Effects of Child and Adolescent Brain and CNS Tumors— Over the last decade, survival rates have slowly improved for children and adolescents diagnosed with brain tumors.<sup>59</sup> Although there is variation by tumor type, today, over 80% of children diagnosed with a CNS tumor of any kind will become a long-term survivor (See Table 8). Brain and CNS tumors in children are generally treated with a multimodal approach including surgery, radiation, and chemotherapy.<sup>60</sup> Unfortunately, many of these survivors will struggle with long-term and late effects affecting multiple organ systems, that are generally attributable to their curative treatment history.

Long-term effects of brain and other CNS tumor treatment can vary by tumor type, location in the brain, and/or extent of neurosurgical intervention. Long-term effects of a CNS tumor diagnosis can include seizures, neuromuscular deficits, visual impairment, hearing loss, difficult behaviors, and neurocognitive disorders.<sup>61</sup>

Late effects of brain or other CNS tumor treatment can occur many months or years after a child or adolescent finishes cancer treatment and are often related to radiation or chemotherapy toxicities. Survivors may experience academic or psychosocial difficulties, as well as systemic disorders such as vasculopathies or cerebrovascular accidents, endocrinopathies, infertility, nephropathy, and increased risk of secondary malignancies later in life.<sup>62</sup> Children diagnosed with a brain or other CNS tumor at a younger age, treated with cranial radiation therapy, and those with tumors involving eloquent regions of the central nervous system have the highest risk of late effects.<sup>63</sup>

Recognition and awareness of the long-term and late effects experienced by childhood and adolescent brain tumor survivors are critical to improving their care and quality of life. Through a better understanding of treatment related morbidity, scientists and clinicians can improve future therapeutic interventions for childhood and adolescent brain and other CNS tumor patients with long-term survival in mind. Pediatric oncologists and dedicated research groups, including the North American based Children's Oncology Group (COG) and the Childhood Cancer Survivor Study (CCSS) are working to improve our understanding of the survivorship experience. More insight can be gained through clinical trial participation and through funding of investigator-initiated research specific to childhood cancer survivors.<sup>64</sup>

### Strengths and Limitations Of Cancer Registry Data

CBTRUS, in collaboration with the CDC and NCI, is the largest population-based registry focused exclusively on primary brain and other CNS tumors in the United States and represents cases collected from the entire US population. The CBTRUS Statistical Report: Pediatric Brain Tumor Foundation Childhood and Adolescent Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2014–2018 contains population-based data on all primary brain tumor and other CNS tumors in children and adolescents ages 0–19 years available through the cancer surveillance system in the United States.

Registration of individual cases is conducted by cancer registrars at the institution where diagnosis or treatment occurs and is then transmitted to the CCR, which further transmits this information to NPCR and/or SEER. CCRs, those contributing data to NPCR and to SEER, only report cases to the CDC and NCI for persons who are residents of that particular state, so duplicate records should not occur for persons who may have traveled across state lines for treatment. As a result, the CBTRUS dataset is a complete recording of all cases submitted to CCR for the time period examined, 2014–2018, with minimal duplicates.

Currently, there is no publicly available data source for the collection of survival and outcomes data from all geographic regions in the United States via the cancer registry system. Survival data used for this report are collected by NPCR for 42 of the 51 CCR in the United States primarily through linkage with death certificate and other administrative records. The remaining CCR are collected by SEER through both active and passive methods. The feasibility of these data for use in survival studies has been evaluated<sup>65,66</sup> and shown to produce reliable and robust estimates of cancer survival. Use of passive follow-up with record linkage may result in overestimation of survival in some populations, such as those that are more likely to leave the state or country.

No mechanism currently exists for central pathology review of cases within the US cancer registry system, and histopathology code assignment at case registration is based on information contained in the patient's medical record. The WHO Classification of Tumours of the Central Nervous System was revised in 1993,67 2000,68 2007,69 2016,5 and 2021.70 As of 2018, the US cancer registry system uses the 2016 classification for data abstraction, but tumors included in this report may have been diagnosed using any of the available classifications prior to 2014 due to the variation in adoption of new standards by individual physicians and medical practices. As a result, histopathologies are reflective of the prevailing criteria for the histopathology at the time of case registration. This means that despite changes to the histopathology schema that may occur over time, it is not possible, without additional variables, to go back and reclassify tumors based on the new criteria. In addition to changes in histopathologic criteria over time, there is significant inter-rater variability in histopathological diagnosis of glioma.<sup>71,72</sup> This also means that incomplete, incorrect, or alternatively stated diagnoses included in a pathology report or other medical record may result in an incorrect reporting of the details of an individual case.

United States cancer registration requires the reporting of cases that are confirmed by different types of diagnostic procedures, including both microscopic confirmation (where surgery was performed and the diagnosis confirmed by a pathologist) and radiographic confirmation (where diagnosis was made based solely on imaging criteria, such as an magnetic resonance imaging (MRI), CT scan, or X-ray). Only microscopic confirmation allows certainty on the assignment of a specific histopathology as well as for an assignment of a WHO grade. Many tumors have unique characteristics that make them identifiable on imaging, and thereby qualify as a valid type of diagnostic procedure, but it is important to consider the decreased level of certainty of specifying the correct histopathology in these tumors.

### **Concluding Comment**

The *CBTRUS* Statistical Report: Pediatric Brain Tumor Foundation Childhood and Adolescent Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2014–2018 comprehensively describes the population-based incidence, mortality, prevalence, and relative survival of primary brain and other CNS tumors in children and adolescents ages 0–19 years collected and reported by CCRs covering the entire US population. This report aims to serve as a useful resource for researchers, clinicians, patients, and families. CBTRUS continually revises its reports to reflect the current collection and reporting practices of the broader surveillance community in which it works, while integrating the input it receives from the clinical and research communities, especially from neuropathologists, when possible.

### **CBTRUS Mission**

CBTRUS is a not-for-profit corporation committed to providing a resource for gathering and disseminating current epidemiologic data on all primary brain and other central nervous system tumors, benign and malignant, for the purposes of accurately describing their incidence and survival patterns, evaluating diagnosis and treatment, facilitating etiologic studies, establishing awareness of the disease, and ultimately, for the prevention of all brain tumors.

### **Supplementary Material**

Supplementary material is available online at *Neuro-Oncology* (http://neuro-oncology.oxfordjournals.org/).

Supplementary Table 1. Central Brain Tumor Registry of the United States (CBTRUS), Brain and Other Central Nervous System Tumor Site Groupings

Supplementary Table 2. Childhood and Adolescent Brain and Other Central Nervous System Tumor Histopathology Groupings (Based on 2016 WHO classification)

Supplementary Table 3. ICD-O-3 Morphology Codes for All Histopathologies Included in Glioma and Embryonal Tumor Childhood and Adolescent Report Major Histopathology Groupings (Based on 2016 WHO Classification)

Supplementary Table 4. Total Cases, Annual Average Cases, Age-Specific Incidence Rates, Total Deaths, Annual Average Deaths, and Age-Specific Mortality Rates, for Brain and Other Central Nervous SystemTumors Ages 0–19 Years by Central Cancer Registry, (CBTRUS: Incidence Data provided by CDC's NPCR and NCI's SEER Program, 2014– 2018; Mortality Data provided by NCHS's NVSS Program, 2014–2018)

Supplementary Table 5. Average Annual Age-Specific Incidence Rates for Brain and Other Central Nervous System Tumors Ages 0–19 Years by Major Histopathology Groupings, Histopathology, Sex, and Age Groups, CBTRUS Childhood and Adolescent Brain Tumor Report: NPCR and SEER, 2014–2018 Supplementary Table 6. Average Annual Age-Specific Incidence Rates for Brain and Other Central Nervous System Tumors Ages 0–19 Years by Major Histopathology Groupings, Histopathology, Race, Hispanic Ethnicity, and Age Group, CBTRUS Childhood and Adolescent Report: NPCR and SEER, 2014–2018

Supplementary Table 7. Annual Percent Change (APC) and 95% Confidence Intervals for Incidence Time Trends in Brain and Other Central Nervous System Tumors by Histopathology Groupings and Age Group, CBTRUS Childhood and Adolescent Report: NPCR and SEER, 2004–2018

Supplementary Table 8. Annual Percent Change (APC) and 95% Confidence Intervals for Cancer Mortality Rates by Cause of Death and Age Group, CBTRUS Childhood and Adolescent Report: NVSS, 1969–2018

Supplementary Table 9. Estimated Prevalent Case Counts and Crude Prevalence Rate per 100,000 for ICCC Defined Cancers Occurring in Locations Other than the Brain or Central Nervous System in Children and Adolescents Ages 0–19 Years at Time of Prevalence in the United States, 2022 Supplementary Table 10. Inherited Syndromes Associated with Childhood and Adolescent Brain and Other Central Nervous SystemTumors, Ages 0–19 Years

Supplementary Table 11. Previously Reported Childhood and Adolescent Brain and Other Central Nervous System Tumors Ages 0–19 Years Risk Loci Identified by Genomewide Association Studies, by Histopathology Including Allele Frequencies, p-values, Odds Ratios (OR) and 95% Confidence Intervals (95% CI)

Supplementary Table 12. A Summary of Recent (2012–2022) Case-control and Cohort Studies Exploring Environmental Exposures and Risk of Childhood and Adolescent Brain and Other Central Nervous System Tumors Ages 0–19 Years

Supplementary Figure 1. Average Annual Age-Specific Incidence Rates per 100,000 Population of Primary Brain and Other Central Nervous System Tumors by Central Cancer Registry and Age Group, in Children and Adolescents Ages A) 0–4 Years, B) 5–9 Years, C) 10–14 Years, and D) 15–19 Years, CBTRUS Childhood and Adolescent Report: US Cancer Statistics—NPCR and SEER, 2014–2018

Supplementary Figure 2. Country- and Age-Specific A) Incidence and B) Mortality Rates per 100,000 Population due to Primary Malignant Brain and Other Central Nervous System Tumors in Children and Adolescents Ages 0–19 Years (From International Agency for Research on Cancer's GLOBOCAN 2020)

Supplementary Figure 3. Distribution in Infants Age < 1 Year of All Primary Brain and Other Central Nervous System Tumors (Five-Year Total = 1,235; Annual Average Cases = 247) by A) Site and B) Histopathology, CBTRUS Childhood and Adolescent Report: US Cancer Statistics— NPCR and SEER, 2014–2018

Supplementary Figure 4. Distribution in Children Ages 1–4 Years of All Primary Brain and Other Central Nervous System Tumors (Five-Year Total = 4,871; Annual Average Cases = 974) by A) Site and B) Histopathology, CBTRUS Childhood and Adolescent Report: US Cancer Statistics— NPCR and SEER, 2014–2018

Supplementary Figure 5. Distribution in Children Ages 5–9 Years of All Primary Brain and Other Central Nervous

System Tumors (Five-Year Total = 5,628; Annual Average Cases = 1,126) by A) Site and B) Histopathology, CBTRUS Childhood and Adolescent Report: US Cancer Statistics—NPCR and SEER, 2014–2018

Supplementary Figure 6. Distribution in Children Ages 10–14 Years of All Primary Brain and Other Central Nervous System Tumors (Five-Year Total = 6,074; Annual Average Cases = 1,215) by A) Site and B) Histopathology, CBTRUS Childhood and Adolescent Report: US Cancer Statistics— NPCR and SEER, 2014–2018

Supplementary Figure 7. Distribution in Adolescents Ages 15–19Years of All Primary Brain and Other Central Nervous System Tumors (Five-Year Total = 7,689; Annual Average Cases = 1,538) by A) Site and B) Histopathology, CBTRUS Childhood and Adolescent Report: US Cancer Statistics— NPCR and SEER, 2014–2018

### Disclaimer

CBTRUS is a not-for-profit corporation which gathers and disseminates epidemiologic data on primary brain and other CNS tumors to facilitate research and establish awareness of the disease. CBTRUS makes no representations or warranties, and gives no other assurances or guarantees, express or implied, with respect to the accuracy or completeness of the data presented. The information provided in this report is not intended to assist in the evaluation, diagnosis, or treatment of individual diseases. Persons with questions regarding individual diseases should contact their own physician to obtain medical assistance. The contents in this report are solely the responsibility of the authors and do not necessarily represent the official views of CDC or of NCI.

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### The CBTRUS Scientific Team

Jill S. Barnholtz-Sloan, Ph.D., CBTRUS Co-Scientific Principal Investigator, Associate Director and Senior Investigator, Center for Biomedical Informatics & Information Technology (CBIIT) and Trans Divisional Research Program (TDRP), Division of Cancer Epidemiology and Genetics (DCEG), National Cancer Institute, Bethesda, MD

Quinn T. Ostrom, Ph.D., M.P.H., CBTRUS Co-Scientific Principal Investigator, Assistant Professor, The Preston Robert Tisch Brain Tumor Center at Duke University Medical Center and Department of Neurosurgery, Duke University School of Medicine, Durham, NC

Gino Cioffi, M.P.H., Trans Divisional Research Program (TDRP), Division of Cancer Epidemiology and Genetics (DCEG), National Cancer Institute, Bethesda, MD

Kristin A. Waite, Ph.D., Trans Divisional Research Program (TDRP), Division of Cancer Epidemiology and Genetics (DCEG), National Cancer Institute, Bethesda, MD

Corey Neff, M.P.H., Department of Neurosurgery, Duke University School of Medicine, Durham, NC

Mackenzie Price, M.P.H., Department of Neurosurgery, Duke University School of Medicine, Durham, NC

### The CBTRUS Consulting Neuropathologists

Daniel J. Brat, M.D., Ph.D., Professor and Chair, Department of Pathology, Northwestern University Feinberg School of Medicine, Chicago, IL

Janet M. Bruner, M.D., MD Anderson Cancer Center, Houston, TX (Retired as of 2020)

Roger E. McLendon, M.D., Professor, The Preston Robert Tisch Brain Tumor Center at Duke University Medical Center and Department of Pathology, Duke University Medical Center, Durham, NC

Tarik Tihan, M.D., Ph.D., Professor, Neuropathology Division, Department of Pathology, School of Medicine, University of California San Francisco (UCSF), San Francisco, CA

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### Selected CBTRUS Scientific Publications focused on Children and Adolescents

Gittleman H, et al. Descriptive epidemiology of germ cell tumors of the central nervous system diagnosed in the United States from 2006 to 2015. J Neurooncol. 2019 Jun;143(2):251–260. doi: 10.1007/s11060–019–03173–4. Epub 2019 Apr 25. PMID: 31025275. *This manuscript details the descriptive epidemiology, including incidence and survival, for germ cell tumors* 

Greppin K, et al. Epidemiology of pineoblastoma in the United States, 2000–2017. Neurooncol Pract. 2022 Jan 27;9(2):149–157. doi: 10.1093/nop/npac009. PMID: 35371520; PMCID: PMC8965073. *This manuscript details the descriptive epidemiology, including incidence and survival, for pineoblastoma.* 

Khanna V, et al. Incidence and survival trends for medulloblastomas in the United States from 2001 to 2013. J Neurooncol. 2017 Dec;135(3):433–441. doi: 10.1007/s11060–017–2594–6. Epub 2017 Aug 21. PMID: 28828582.

This manuscript details the descriptive epidemiology, including incidence, survival, and time trends, for medulloblastoma in children and adolescents.

Ostrom QT, et al. Pilocytic astrocytomas: where do they belong in cancer reporting? Neuro Oncol. 2020 Feb 20;22(2):298– 300. doi: 10.1093/neuonc/noz202. PMID: 31637436; PMCID: PMC7442407.

This letter describes the history of inclusion of pilocytic astrocytoma in cancer registry reporting, and the effect of varying behavior classification for these tumors on incidence and survival patterns.

Patil N, et al. Epidemiology of Brainstem High-Grade Gliomas in Children and Adolescents in the United States, 2000–2017. Neuro Oncol. 2020 Dec 21:noaa295. doi: 10.1093/neuonc/ noaa295. PMID: 33346835.

This manuscript details the descriptive epidemiology, including incidence, survival, and prevalence, for gliomas of the brain stem in children and adolescents.

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