Multi-institutional study of the frequency, genomic landscape, and outcome of IDH-mutant glioma in pediatrics

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Abstract

Background. The incidence and biology of *IDH1/2* mutations in pediatric gliomas are unclear. Notably, current treatment approaches by pediatric and adult providers vary significantly. We describe the frequency and clinical outcomes of *IDH1/2*-mutant gliomas in pediatrics.

Methods. We performed a multi-institutional analysis of the frequency of pediatric *IDH1/2*-mutant gliomas, identified by next-generation sequencing (NGS). In parallel, we retrospectively reviewed pediatric *IDH1/2*-mutant gliomas, analyzing clinico-genomic features, treatment approaches, and outcomes.

Results. Incidence: Among 851 patients with pediatric glioma who underwent NGS, we identified 78 with *IDH1/2* mutations. Among patients 0–9 and 10–21 years old, 2/378 (0.5%) and 76/473 (16.1%) had *IDH1/2*-mutant tumors,

respectively. Frequency of IDH mutations was similar between low-grade glioma (52/570, 9.1%) and high-grade glioma (25/277, 9.0%). Four tumors were graded as intermediate histologically, with one *IDH1* mutation.

Outcome: Seventy-six patients with *IDH1/2*-mutant glioma had outcome data available. Eighty-four percent of patients with low-grade glioma (LGG) were managed observantly without additional therapy. For low-grade astrocytoma, 5-year progression-free survival (PFS) was 42.9% (95%CI:20.3–63.8) and, despite excellent short-term overall survival (OS), numerous disease-related deaths after year 10 were reported. Patients with high-grade astrocytoma had a 5-year PFS/OS of 36.8% (95%CI:8.8–66.4) and 84% (95%CI:50.1–95.6), respectively. Patients with oligodendroglioma had excellent OS.

Conclusions. A subset of pediatric gliomas is driven by *IDH1/2* mutations, with a higher rate among adolescents. The majority of patients underwent upfront observant management without adjuvant therapy. Findings suggest that the natural history of pediatric *IDH1/2*-mutant glioma may be similar to that of adults, though additional studies are needed.

Key Points

- *IDH1/2* mutations are present in a subset of pediatric glioma, validating prior data.
- Most pediatric patients with IDH-mutant LGG are observed without adjuvant treatment at study institutions.
- Long-term outcomes of pediatric and adult IDH-mutant glioma are similar.

Importance of the Study

IDH1/2 mutations have traditionally been considered rare in pediatric glioma, with a paucity of clinical data in this population. In contrast, such mutations have commonly been described in adult gliomas and are typically associated with gliomagenesis and progression to higher grade. Importantly, the treatment approaches adopted by pediatric and adult oncologists tend to differ significantly, with unclear impact on outcomes. In this study, we systematically evaluate the frequency, treatment approaches, and outcomes of pediatric patients with *IDH1/2*-mutant glioma. We show that a significant proportion of pediatric gliomas harbor *IDH1/2* mutations and most patients were managed observantly without adjuvant therapy, unlike their adult counterparts. However, long-term outcomes in pediatrics were similar to those reported in adult studies, supporting a role for adaptation and incorporation of adult treatment approaches in pediatric cases.

Gliomas are the most common primary central nervous system (CNS) tumor in children.[1] Despite histological similarities to adult tumors, pediatric gliomas are often clinically and molecularly distinct. Children diagnosed with conventional pediatric low-grade glioma (LGG) have an excellent prognosis.[2] Contrastingly, the majority of adult LGGs ultimately undergo malignant transformation to HGGs with poorer prognosis.[2,3] A key driver in this difference in clinical behavior is the fact that pilocytic astrocytoma is the most common glioma in the pediatric population, and comprises 17.6% of all pediatric brain tumors.[1] Overall, pediatric LGGs, whether circumscribed or diffuse, are typically driven by activating alterations in the MAPK pathway (such as the *KIAA1549::BRAF* fusion observed in pilocytic astrocytoma). In contrast, adult LGGs are classically characterized by *IDH1/2* mutations with frequent cooccurring alterations.[4–6] This has led the 5th edition of the WHO Classification of CNS tumors to distinguish between "pediatric type" and "adult type" tumors, with IDH-mutant gliomas considered one of the adult types.[7]

While *IDH1/2* mutations were traditionally considered rare in pediatric glioma, recent studies report a wide possible range of frequency from 1% to 20%, with higher rates in adolescence.[8–12] Furthermore, the prognostic significance of *IDH1/2* mutation in the pediatric population is not fully understood. This has critical clinical implications, as the treatment approach for LGGs differs significantly between adults and pediatrics. Radiation therapy (RT) is often delayed or avoided in children and adolescents due to its associated long-term toxicities.[13,14]

For older adults, multimodal therapy is considered standard-of-care, with initial maximal safe resection followed by irradiation and chemotherapy. This practice is based on prospective trials showing improved outcomes with these approaches, especially among patients with residual tumor after upfront resection.[15–17] Observant management is typically limited to younger patients with complete resections and favorable genomics. The pediatric oncology community has not generally adopted these practices given the paucity of data surrounding pediatric IDH-mutant glioma.

It is unclear if *IDH1/2* mutations occurring in children and adolescent with gliomas confer similar prognostic significance to warrant such an aggressive upfront approach. In this multi-institutional, retrospective investigation, we sought to determine the frequency of *IDH1/2* mutation among pediatric gliomas, and to describe the clinicopathologic features, genomic landscape, and efficacy of current treatment approaches. This study aims to improve our understanding of this disease and aid in establishing best practices for this age group.

Methods

This study includes two parallel analyses with distinct objectives and methodologies. One part involved five collaborating institutions to evaluate the overall frequency of *IDH1/2*-mutant glioma in pediatrics (sequencing cohort). The second part involved nine collaborating sites and aimed to evaluate the clinical features, treatment, genomics, and outcomes of pediatric patients with IDH-mutant glioma (clinical cohort). The institutional review board for each site approved this retrospective review (DF/HCC protocol 19-548).

Frequency of *IDH1/2*-mutant Glioma in the Pediatric Population (Sequencing Cohort)

The frequency of *IDH1/2*-mutant glioma in the pediatric population was determined by evaluating *IDH1/2*-mutational frequency through next-generation sequencing (NGS) of gliomas among patients under 21 years. This multi-institutional collaboration included four children's hospitals or cancer centers [Children's Hospital of Philadelphia (CHOP), Children's Hospital Los Angeles (CHLA), Dana-Farber Cancer Institute/Boston Children's Hospital (DFCI/BCH), Memorial Sloan Kettering Cancer Center (MSKCC)] and an industry partner (Tempus Labs, Inc.). These sites were chosen for this part of the study specifically because they utilized established NGS platforms and have routinely sequenced all gliomas (including pilocytic astrocytoma) during the noted study timeframes. All NGS platforms included unique cancer gene panels that included hotspot coverage of both *IDH1* and *IDH2* genes. A list of all genes tested on each individual platform and timeframe of testing is available in Figure 1A, Supplementary Table 1, respectively.

Collaborators identified the number of *IDH1/2*-mutant gliomas in their respective cohorts over a specified timeframe and contributed data for their respective cohorts as it related to histological grade, subtype, and coexisting mutations/alterations. Timeframes included in the study varied by site (Figure 1A).

The frequency of *IDH1/2*-mutant glioma is reported as a fraction of all sequenced pediatric gliomas (encompassing all histologic grades, including circumscribed gliomas) as the denominator. Our methodology to determine the institution-specific and overall frequency of *IDH1/2*-mutant glioma is shown in Supplementary Figure 1.

Clinical Features and Outcome Data for Pediatric *IDH1/2*-mutant Glioma (Clinical Cohort)

To evaluate the clinical features and outcome data for pediatric *IDH1/2* mutant glioma, we employed a multi-institutional retrospective approach with collaborators across nine institutions (CHOP, CHLA, OHSU Doernbecher Children's Hospital, Orlando Health Arnold Palmer Hospital for Children, Lurie Children's Hospital, Children's Healthcare of Atlanta, St. Louis Children's Hospital-Washington University, MSKCC, DFCI/BCH).

Patient selection
Using respective institutional databases, all patients with glioma diagnosed before the age of 21 years between 1990 and 2020 were identified. Patient selection timeframe was extended to 1990 to capture patients who may have been diagnosed with an *IDH1/2* mutation at the time of recurrence. Patients treated at their respective institutions during that time were eligible for the clinical cohort if they had *IDH1* or *IDH2* mutation detected by immunohistochemistry and/or sequencing and had clinical follow-up data.

Data collection and analysis
Patient demographics, clinicopathological diagnosis, molecular features, clinical course, and outcomes were extracted from the medical record. All clinical data were de-identified at individual collaborating sites prior to secure, electronic data transfer between sites via Research Electronic Data Capture (REDCap).[18]

Progression-free survival (PFS) was calculated from date of diagnosis to date of disease progression. Overall survival (OS) was calculated from the date of diagnosis to date of death. Patients alive and/or without disease progression were censored at last follow-up. Both OS and PFS were estimated according to the Kaplan–Meier method, and differences in survival were assessed using the log-rank test.
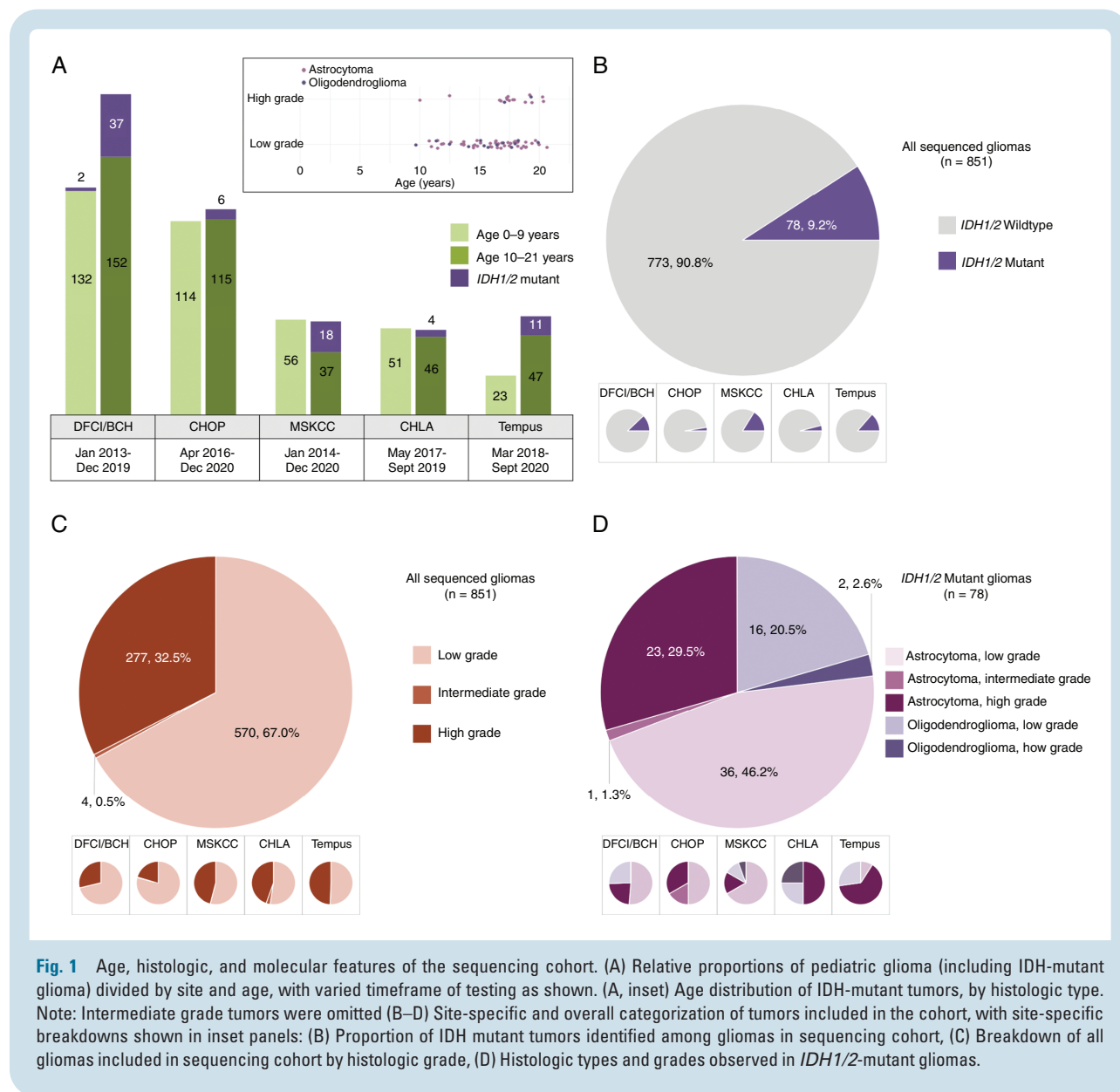
Molecular features
Targeted NGS reports from respective institutions were analyzed for single nucleotide variants, indels, copy number variants (CNVs), and structural variants. Gene-level CNVs were not consistently reported among participating institutions, but this data was included when available. Reports from microarray-based comparative genomic hybridization were used to further evaluate CNVs in cases when available. All Tier 1, 2, and 3 alterations were collated and visualized using OncoPrint in the "ComplexHeatmap" package in R (v3.6). Only genes assayed in 80% of the samples were used for all subsequent analyses.

Results

Frequency of *IDH1/2*-mutant Glioma in the Pediatric Population (Sequencing Cohort)

We identified 851 patients with gliomas between the ages of 0–21 years whose tumor samples underwent

Fig. 1 Age, histologic, and molecular features of the sequencing cohort. (A) Relative proportions of pediatric glioma (including IDH-mutant glioma) divided by site and age, with varied timeframe of testing as shown. (A, inset) Age distribution of IDH-mutant tumors, by histologic type. Note: Intermediate grade tumors were omitted (B–D) Site-specific and overall categorization of tumors included in the cohort, with site-specific breakdowns shown in inset panels: (B) Proportion of IDH mutant tumors identified among gliomas in sequencing cohort, (C) Breakdown of all gliomas included in sequencing cohort by histologic grade, (D) Histologic types and grades observed in *IDH1/2*-mutant gliomas.

NGS. Seventy-eight patient tumor samples harbored *IDH1/2* mutations, accounting for 9.2% (78/851) of the entire cohort. Among these *IDH1/2*-mutant gliomas, 52 were histologically LGGs (WHO grade 1 & 2), comprising 9.1% (52/570) of all pLGG patients (*n* = 570). Twenty-five *IDH1/2*-mutant tumors were histologically HGGs (WHO 3 & 4), accounting for 9.0% (25/277) of all pHGG patients (*n* = 277). Pathologists designated four gliomas as intermediate grade (features indeterminate between low- and high-grade) that included one *IDH1* mutation. Children aged 0–9 years accounted for 44.4% (378/851) of sequenced pediatric gliomas, of which only two possessed *IDH1/2* mutations (2/378; 0.5%). Adolescents aged 10–21 years accounted for 55.6% (473/851) of the pediatric gliomas sequenced, with 76 *IDH1/2*-mutant tumors (76/473; 16.1%). Detailed analysis of data obtained from each institution is listed in Figure 1, Supplementary Table 2 and 3.

Patient Characteristics (Clinical Cohort)

In the clinical cohort, a total of 76 pediatric patients with *IDH1/2* mutant gliomas were identified among the nine participating sites. Median age at diagnosis was 16.8 years (range: 9.7–20.7 years). Sixty-one patients were diagnosed with astrocytoma, while 15 patients were diagnosed with oligodendroglioma (with 1p/19q codeletion).

Most tumors were supratentorial (*n* = 72), with only four tumors occurring in the posterior fossa (three brainstems, one cerebellar). None were reported in the suprasellar region, basal ganglia, thalamus, or spine. The majority of tumors were histologically low-grade [WHO grade 2 (58/76; 76.3%)]. One tumor was assigned an intermediate grade, and the remaining patients had high-grade tumors [WHO grade 3–4 (17/76; 22.4%)]. For patients with *IDH1*-mutant tumors, the canonical R132H was the most common alteration (61/68; 89.7%), followed by R132C (5/68; 7.4%), and

R132S (2/68; 2.9%). For *IDH2*-mutant tumors, R172K and R172M were most common. All four posterior fossa tumors were HGGs, with two harboring the noncanonical R132C mutation.

All patients underwent an upfront surgical procedure for diagnostic and/or therapeutic indications. Thirty-one patients (31/76; 40.8%) underwent gross-total resections (GTR), 33 patients (33/76; 43.4%) had subtotal resections (STR), and 12 patients (12/76; 15.8%) had biopsies (Bx) only. Following surgery, 50/76 patients (65.8%) underwent expectant observation without additional adjuvant therapy. Of these patients, all but one had low-grade histology. Twenty-two patients (22/76; 28.9%) received upfront RT, with a median focal radiation dose of 5940 cGy (range:5400–6000). Most of the patients who received upfront RT had high-grade histology (16/22; 72.7%). Upfront chemotherapy was administered to a subset of patients (23/76; 30.2%). Of these, 19 patients received upfront RT followed by chemotherapy, 15 of whom had HGGs, three with LGGs, and one with intermediate grade histology. Patient characteristics, sorted by histologic type, are summarized in Table 1.

Clinical Outcomes (Clinical Cohort)

For the entire clinical cohort of pediatric *IDH1/2*-mutant gliomas (*n* = 76), which includes both astrocytoma and oligodendroglioma, with a median follow-up period of 4.0 years [range:0.2–32.4 years (IQR:2-7.5 years)], the 5- and 10-year PFS rates were 44.5% (95%CI:28.6–59.2) and 18.7% (95%CI:5.8–37.8), respectively; The 5- and 10-year OS rates were 92% (95%CI:79.3–96.6) and 78.2% (95%CI:59.7–88.5), respectively (Figure 2A). While histological grade was not associated with altered PFS [median survival: 4.8 (LGG) vs 4.4 years (HGG); *P* = .71 (Supplementary Figure 2A)], LGGs were associated with significantly better OS, with 5- and 10-year OS of 96.4% (95%CI:81.1–99.3) and 92.1% (95%CI:72.6–97.8), compared to 75.1% (95%CI:39.8–91.4) and 19.7% (95%CI:0.7–57.1) for HGGs, respectively [*P* < .0001 (Figure 2B)].

IDH1/2-mutant Astrocytoma

For pediatric *IDH1/2*-mutant astrocytoma (*n* = 61), with a median follow-up period of 3.8 years (range:0.2–25.3), the 5- and 10-year PFS were 40.5% (95%CI:22.2–58.4) and 0%, respectively. The 5-, 10-, and 15-year OS were 92.9% (95%CI:79.4–97.5), 73.1% (95%CI:49.5–86.8), and 30.3% (95%CI:5.2–61.6), respectively (Figure 2C). Median PFS was 4.7 years, while the median OS for this cohort was 11.7 years. Histological grade did not significantly affect the PFS, with median PFS of 4.8 years for low-grade and 4.4 years for high-grade [*P* = .67, (Figure 2D)]. In contrast, high histological grade was associated with significantly shorter OS, with 5- and 10-year OS for high-grade tumors of 84% (95%CI:50.1–95.6) and 22.2% (95%CI:0.9–61.3), respectively, as compared to 95.4% (95%CI:74.5–99) and 88.6% (95%CI:61.2–97) for low-grade tumors (Figure 2E). This translates to a median OS for low-grade and high-grade *IDH1/2*-mutant astrocytoma of 12.5 and 6.4 years, respectively (*P* < .0001).

Outcomes for patients managed observantly (low-grade astrocytoma)

Most patients with low-grade diffuse astrocytoma underwent expectant observation without additional adjuvant therapy after initial surgery (39/45; 86.7%), including 20 patients (20/39; 51.3%) who underwent STR/Bx only. Among these 39 patients, the 5- and 10-year PFS was 41.7% (95%CI:17.5–64.7) and 0%, respectively, with a median PFS of 4.76 years. While OS for this observation-only cohort was 100% at 10 years with a median OS of 18.9 years, numerous deaths due to disease progression after year 10 were noted (Figure 2F). Interestingly within this cohort, extent of resection did not significantly impact survival outcomes [*P* = .51 (PFS) and *P* > .99 (OS)].

Impact of extent of upfront resection (low-grade astrocytoma)

Among all patients with low-grade astrocytoma (*n* = 45), upfront extent of resection was not associated with statistically significant improvement in survival outcomes. The 5-year PFS for patients with GTR was 45.7% (95%CI:8.5–77.6) with a median PFS of 4.4 years, while the 5-year PFS for patients with STR/Bx was 41% (95%CI:14.6–65.9) with a median PFS of 4.7 years (*P* = .4). In contrast, patients with GTR showed a trend towards better OS, with a 10-year OS of 100% compared to a 10-year OS of 81.3% (95%CI:41.6–95.2) for patients with STR/Bx (*P* = .23).

Impact of radiation (low-grade astrocytoma)

Only four patients with low-grade astrocytoma received upfront RT. At a median follow-up period of 1.94 years (range:0.7–5.7), none experienced disease progression/recurrence at time of last follow-up. Among the 41 patients who did not receive upfront RT, with a median follow-up period of 4 years (range:0.8–25.3), the 5-year PFS was 38.8% (95%CI:16.3–61.2) with a median PFS of 4.5 years [*P* = .28 (Figure 2G)].

Five patients with recurrent/progressive low-grade astrocytoma without progression to high-grade received radiation therapy at first progression [median time-to-progression: 2.5 years (range:0.8–6.8)]. Median follow-up period after RT was 8 years (range:3.5–9.7) with 5-year post-RT PFS and OS of 100%.

Impact of surgery on outcome for high-grade astrocytoma

In terms of upfront treatment for patients with high-grade astrocytoma (*n* = 15), better extent of resection showed a trend towards better PFS with a median of 7.5 years among patients receiving GTR compared to 4 years among patients with STR/Bx [*P* = .089 (Supplementary Fig. 2B)]. This translates to 5-year PFS of 66.4% (95%CI:5.2–94.3) among patients with GTR, while patients with STR/Bx had 5-year PFS of 19.9% (95%CI:0.7–57.6). Extent of resection did not significantly impact OS, with median OS of 8.6 for GTR vs 7.1 years for STR/Bx (*P* = .235).

IDH1/2-mutant Oligodendroglioma

Patients with *IDH1/2* mutant oligodendroglioma (*n* = 15) had a median follow-up period of 7.5 years (range:1.5-32.4). Within this group, the 5- and 10-year PFS was 52%

Table 1 Patient Characteristics for Clinical Cohort

| Age at Diagnosis (years; *N* = 76)		
Median	16.8	
Range	9.7 – 20.7	
Tumor Type	**Astrocytoma (*N* = 61)**	**Oligodendroglioma (*N* = 15)**
Age at Diagnosis	16.8 [range: 10.0–20.7]	16.7 [range:9.7–19.9]
Tumor Location	***N* (%)**	***N* (%)**
Supratentorial	57	15
Posterior Fossa (cerebellum/brain stem)	4	0
WHO Grade		
2	45 (73.8)	13 (86.7)
3	12 (19.7)	2 (13.3)
4	3 (4.9)	
Intermediate (2-3)	1 (1.6)	
IDH1/2 Mutation		
IDH1		
R132H	49 (87.5)	12 (100.0)
R132C	5 (8.9)	0 (0.0)
R132S	2 (3.6)	0 (0.0)
IDH2		
R172K	0 (0.0)	3 (100.0)
R172M	3 (60.0)	0 (0.0)
R172G	1 (20.0)	0 (0.0)
Other	1 (20.0)	0 (0.0)
Sequencing Results Available	52 (85.2)	10 (66.7)
MGMT Status		
Methylated	8	1
Partially methylated	1	1
Unmethylated	9	1
Unknown	43	12
Extent of Resection		
Biopsy	10 (16.4)	2 (13.3)
STR	27 (44.3)	6 (40.0)
GTR	24 (39.3)	7 (46.7)
Upfront Radiation		
Yes	19 (31.7) [14 HG, 4 LG, 1 intermediate]	3 (18.7) [2 HGG, 1 LG]
Upfront Radiation Dose (Median cGy)	5940 [Range: 5400–6000]	5940 [Range: 5940–6000]
Upfront Chemotherapy		
Yes	19 (31.7)	4 (25.0)
Temozolomide-based	18	1
Carboplatin/Vincristine	1	1
PCV	0	2
Cycles of Chemotherapy (Median)	12 [range: 0.5–19]	13 [range: 6–18]
Upfront Observant Management	40 (65.6)	10 (66.7)
Low-grade (WHO grade 2)	39	10
Intermediate (WHO grade 2-3)	0	N/A
High-grade (WHO grade 3 & 4)	1	0
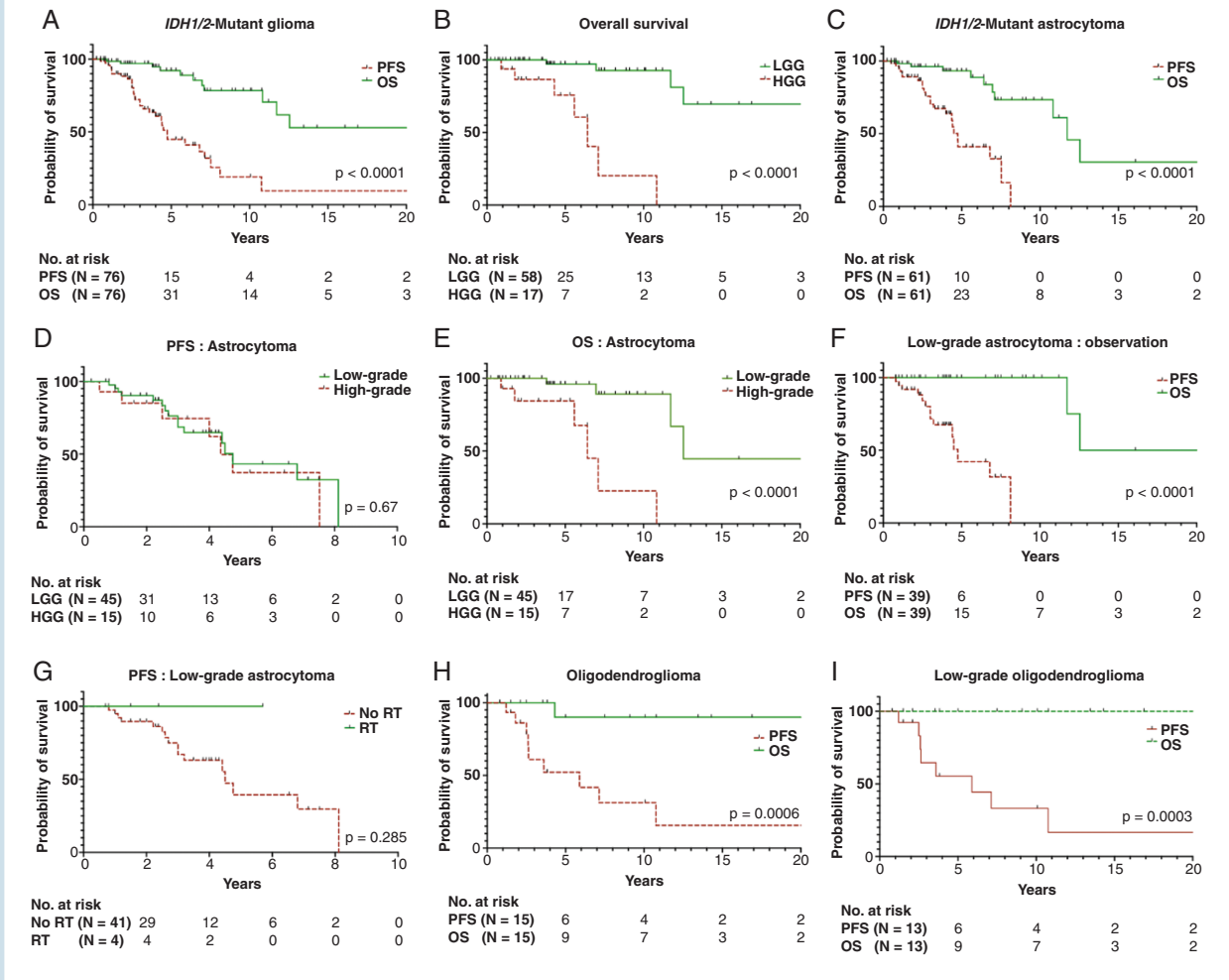
Fig. 2 Progression-free and overall survival of (A) the entire cohort, (C) *IDH1/2*-mutant astrocytoma, (F) Low-grade astrocytoma observed up-front, (H) *IDH1/2*-mutant oligodendroglioma, and (I) Low-grade oligodendroglioma. Overall survival according to grade (low versus high) of (B) entire cohort and (E) astrocytoma. Progression-free survival of (D) astrocytoma according to grade (low/high) and (G) low-grade astrocytoma according to radiation therapy status.

(95%CI:22.2–75.1) and 31% (95%CI:7.8–58.2), while the 5-, 10- and 15-year OS were all 89.8% (95%CI:47–98.2) (Figure 2H).

Outcome for low-grade oligodendroglioma
With a median follow-up of 9.1 years (range:1.5–32.4), these 13 patients had a 5- and 10-year PFS of 55% (95%CI:23.1–78.2) and 33.2% (95%CI:8.1–60.9), respectively, with a median PFS of 5.9 years (Figure 2I). All but one patient remained alive at the time of last follow-up (20-year OS of 100%; Figure 2I). Six patients had GTR upfront, while seven patients received STR or Bx at initial surgery. Extent of resection was not associated with significantly improved outcomes: GTR was associated with a 5- and 10-year PFS of 59.4% (95%CI:12.3–87.9) and 59.4% (95%CI:12.3–87.9) with a median PFS of 10.7 years, while STR/Bx led to a 5- and 10-year PFS of 51.1% (95%CI:11.4–81) and 16.8% (95%CI:0.7–52.4), respectively, with a median PFS of 5.9 years ($P = .43$).

Outcome for anaplastic oligodendroglioma
For the two patients with anaplastic oligodendroglioma, one was diagnosed at age 17.1 and the other at 19.3 years. Both patients received focal RT upfront followed by adjuvant chemotherapy. The patient who underwent upfront STR followed by RT and adjuvant temozolomide progressed after 1.8 years and ultimately died from disease 4.3 years after initial diagnosis. The other patient underwent upfront GTR followed by RT and adjuvant PCV for 6 cycles. This patient remains alive without evidence of disease 2.5 years after initial diagnosis.

Impact of Progression to Higher Histologic Grade

Among patients with low-grade histology ($n = 58$), 25 patients recurred/progressed. At first or subsequent disease progression, 6/16 (37.5%) astrocytomas and 3/9 oligodendrogliomas (33.3%) showed histologic high-grade features at recurrence. Of these 9 patients with progression

to high-grade histology, only one with oligodendroglioma had received upfront RT at diagnosis (recurring 30.5 years later). The other eight patients had been treated with an upfront radiation-sparing approach. Additionally, only one of these patients had GTR upfront; the others had either STR (*n* = 6) or Bx (*n* = 2).

Median time-to-progression to high-grade for astrocytoma was 5.3 years (range:1.1–11.5), while the time-to-progression to high-grade for oligodendroglioma was 14.3 years (range:10.9–30.5). Upon progression to high-grade, all patients received RT. With a median follow-up of 3.1 years (range:1.9–4.3) after RT for the six patients with astrocytoma, 1-year PFS and OS were both 100%, while 3-year PFS and OS were 44.1% (95%CI:6.3–78.2) and 62.2% (95%CI:13.7–88.9), respectively. Of the three patients with oligodendroglioma, two remain alive at 5.2 and 2.3 years after progression to high-grade and RT. The one patient who received upfront radiation therapy progressed quickly following transformation and died of disease 1.9 years later despite re-irradiation.

Genomic Landscape (Clinical Cohort)

Comprehensive molecular reports were available for 62 of 76 patients in this cohort. Molecular analysis revealed numerous alterations cooccurring with *IDH1/2* mutations (Figure 3, Supplementary Figure 3). In patients with astrocytoma, *TP53* mutations were most frequent, identified in 92.3% (48/52) of cases, followed by alterations in *ATRX* (52.9%, 27/51), *ATM* (21.6%, 11/51), *BRCA1/2* (20.0%, 10/50), *MET* (19.6%, 10/51), *SMO* (19.2%, 10/52), *BRAF* (17.3%, 9/52), *CDKN2A/B* (17.3%, 9/52), *SOX2/9* (16.3%, 8/49), *DIS3* (16.3%, 7/43), *MSH2/6* (16.0%, 8/50), and *ARID1A/B* (16%, 8/50) (Supplementary Table 4). While

oligodendrogliomas harbored copy number losses associated with chromosomal 1p/19q-codeletion in numerous genes (e.g., *MUTYH*, *MPL*, *NOTCH2*), additional mutations were observed most frequently in the *TERT* promoter region (40.0%, 4/10) and *CIC* (40.0%, 4/10). Notably, most *BRAF* alterations were copy number gains (*n* = 8/9, 88.9%) associated with gains in *MET* and/or *SMO*. These *BRAF* gains were part of broad 7q gains in all but one case. In addition, most of the *CDKN2A/B* alterations were single-copy deletions (*n* = 6/9, 66.7%).

To evaluate the impact of genetic alterations on outcomes, we first performed univariate time-to-event analyses on genes altered in more than 10% of the cohort. Notably, OS was significantly decreased in tumor samples harboring *CDKN2A/B* deletions (*P* < .001) or alterations in *SMO* (*P* < .0001), *BRCA1/2* (*P* < .01), *MSH2/6* (*P* < .01), *ATRX* (*P* < .05), or *DIS3* (*P* < .05). There was also a trend towards reduced patient OS in samples having *MET* amplifications (*P* = .07) and *ATM* alterations (*P* = .08) (Table 2). Consistent with these results, both *CDKN2A/B* deletions and alterations in *SMO*, *MET*, *BRAF*, or *ATRX* alterations were more common in HGGs. *ATRX* alterations were also more likely to be found in older patients (Supplementary Table 5). In our analysis, only *ATM* (*P* < .05) and *SOX2/9* alterations (*P* < .01) were associated with reduced PFS (Table 2). While these outcome-associated genes were relatively abundant in astrocytomas, no oligodendroglioma harbored *SMO*, *BRCA1/2*, *ATRX*, *DIS3*, *ATM*, or *SOX2/9* alterations, and only one tumor had a *CDKN2A/B* deletion or *MSH2/6* alteration (Figure 3).

To explore whether these outcome-associated genes were predictors of survival specifically rather than molecular markers for high-grade tumors, we next implemented Cox proportional hazards models on OS and PFS while adjusting for WHO grade (Supplementary Table 6). Notably,
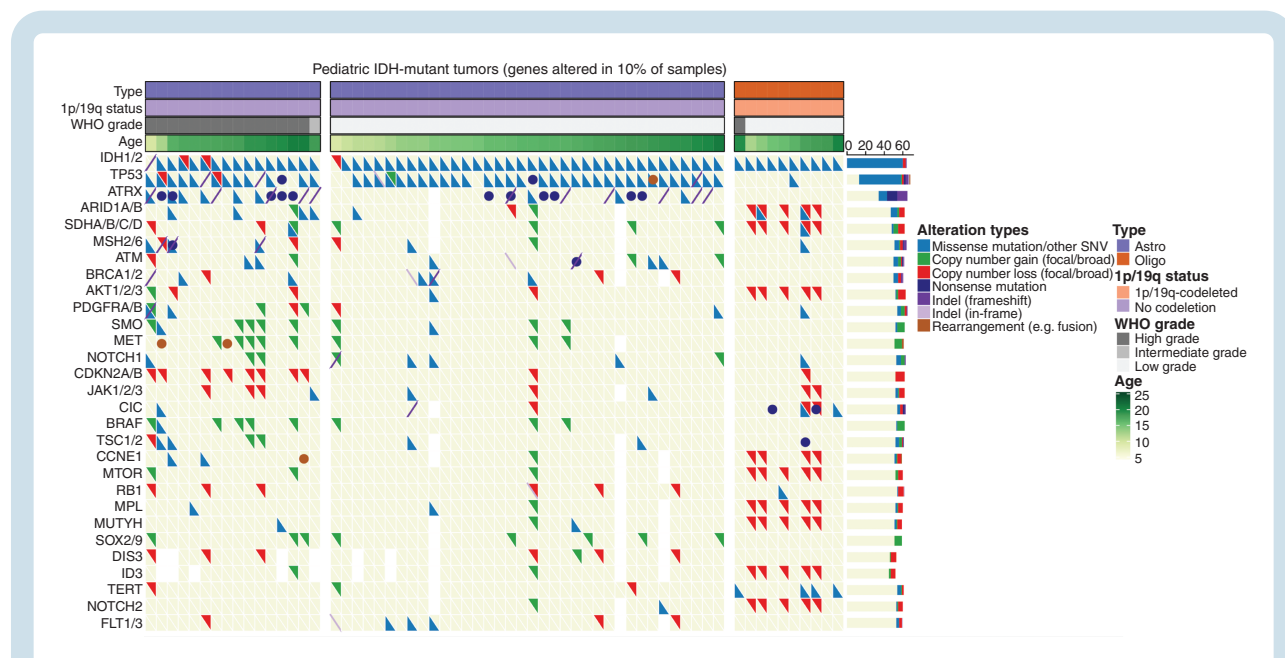

Fig. 3 Comutation plot displaying clinical features and molecular characteristics of 62 patients with pediatric *IDH1/2*-mutant glioma. Shown here are genes altered in at least 10% of the total sample, with the relative incidence (%) of coalterations.

Table 2 Univariate Time-to-event Analyses of Specific Genetic Alterations

Gene	Med. OS (Altered)	Med. OS (Unaltered)	P-value (OS)	Med. PFS (Altered)	Med. PFS (Unaltered)	P-value (PFS)
SMO	6.69	32.36	3.06E-05	2.6	4.5	0.101
CDKN2A/B	6.97	NA	0.000348	4	6.8	0.234
MET	7.1	32.4	0.00247	4.75	4.5	0.427
BRAF	9.07	32.36	0.0034	4.75	4.41	0.462
BRCA1/2	10.8	32.4	0.00522	4.75	4.41	0.541
MSH2/6	6.97	NA	0.00694	2.6	4.5	0.43
ATRX	11.7	32.4	0.0174	4.5	4.41	0.201
DIS3	6.97	32.36	0.0402	4.76	4.5	0.538
MET (amplifications)	9.35	32.36	0.0687	4.76	4.41	0.921
ATM	6.97	32.36	0.0815	2.6	4.76	0.0172
PDGFRA/B	6.97	NA	0.112	2.6	4.76	0.34
MUTYH	32.4	11.7	0.173	10.75	4.41	0.0648
NOTCH2	32.4	11.7	0.18	10.75	4.41	0.12
TSC1/2	6.97	12.54	0.197	2.6	4.5	0.855
TP53	11.7	32.4	0.216	4.5	4.75	0.362
NOTCH1	6.97	12.54	0.332	2.16	4.75	0.338
RB1	12.5	32.4	0.359	2.6	4.5	0.141
TERT	32.4	NA	0.372	2.6	4.75	0.302
MPL	32.4	11.7	0.481	4.76	4.41	0.269
FLT 1/3	NA	32.4	0.505	2.5	4.5	0.36
SOX2/9	NA	12.5	0.546	2.71	4.76	0.00506
ID3	32.4	11.7	0.548	4.76	4.41	0.183
AKT1/2/3	12.5	11.7	0.577	4.75	4.41	0.586
CCNE1	32.4	NA	0.781	4.76	4.5	0.175
ARID1A/B	32.4	11.7	0.794	4.76	4.41	0.264
CIC	32.4	NA	0.893	3.6	4.75	0.62
SDHA/B/C/D	32.4	11.7	0.932	2.63	4.5	0.855
MTOR	32.4	11.7	0.935	4.75	4.41	0.336
JAK1/2/3	12.5	NA	0.966	3.52	4.75	0.867

only alterations in *SMO* (*P* < .001) and *BRAF* (*P* < .01) remained significant predictors of OS in this multivariate analysis, with a trend towards reduced OS for *CDKN2A/B* loss (*P* = .09). However, both *ATM* (*P* < .05) and *SOX2/9* (*P* < .01) alterations remained associated with reduced PFS even when adjusting for grade.

Discussion

Advanced genomic testing has deepened our understanding of cancer biology and allowed for molecular risk stratification of CNS tumors.[19–22] *IDH1/2* mutations, for example, were identified in adult diffuse glioma in the 2000s and associated with superior outcomes compared to IDH-wildtype gliomas.[4,5,23] While previously thought to be rare, *IDH1/2* mutations have in recent years been shown to occur at a substantial rate in the pediatric population.[8–12]

To systematically evaluate the frequency of *IDH1/2* mutation among pediatric gliomas, we amassed a large patient cohort through a multi-institutional collaboration. All collaborators utilized distinct sequencing platforms and in recent years routinely sequence every newly diagnosed CNS tumor. Our cohort of 851 sequenced pediatric gliomas demonstrated *IDH1/2* mutations in nine percent of cases overall, with most cases identified among patients older than ten years. Among adolescents 10–21 years of age, our cohort reveals an incidence rate of approximately 16%, while children under ten years old had an incidence rate of less than 1%, which are within the range of previous reports.[10,12,23–25] Our study is also concordant with observations from Children's Oncology Group that *IDH1* mutations are common in adolescents, and importantly, our data supports the findings of that study that IDH-mutant HGGs have a significantly more favorable prognosis when compared to IDH wild-type HGGs.[12] Conversely, the overall incidence rate observed among pediatric LGGs in our study appears to be higher than several previous publications.[11,26,27] These findings highlight the importance of routine testing for *IDH1/2* mutations and coexisting mutations

in pediatric gliomas, especially among older children with diffuse gliomas.

To describe the clinical features, current treatment approaches, and outcomes within the pediatric population, we utilized a parallel multi-institutional collaboration, where we identified 76 patients across nine institutions. To our knowledge, this represents the largest pediatric *IDH1/2*-mutant glioma cohort with comprehensive clinical data published to date. We showed that most pediatric patients diagnosed with *IDH1/2*-mutant glioma have low-grade histology and a preponderance of astrocytic (nonoligodendroglial) tumors, consistent with the previously established age distribution and incidence for these tumor types. As expected, histological grade was associated with poorer OS; most patients with high-grade astrocytoma died of their disease within 10 years of diagnosis. Most patients with low-grade histology were managed observantly regardless of extent of resection. In contrast, adult patients are typically only observed without adjuvant therapy if they were younger, clinically well, and underwent upfront gross total tumor resection.[28–30]

In our mixed cohort of 39 patients with low-grade astrocytoma who were observed upfront, the median PFS was 4.76 years with a 5- and 10-year PFS of 41.7% and 0%, respectively. These results mirror the outcomes reported for adult patients treated with upfront RT on the RTOG 9802 protocol.[15,31,32] Additionally, the OS for this upfront observation cohort was 100% at ten years. Although these survival data appear more favorable than those reported for adults, numerous disease-related deaths after year 10 were noted. Only four patients with IDH-mutant LGG received upfront radiation, making any conclusions regarding its impact challenging. Five patients with recurrent/progressive IDH-mutant low-grade astrocytoma (without progression to higher grade), who were initially observed, received RT at first recurrence and experienced excellent long-term outcome (5-year PFS and OS at 100%, median follow-up 8 years). This raises the question of whether a patient could strictly be observed until recurrence and then receive irradiation as a radiation-delaying approach without compromising outcome.

For patients with low-grade oligodendroglioma, the median PFS at 5.9 years is comparable to the cohort treated with upfront RT on the RTOG 9802 protocol.[15,31] However, ten out of our thirteen patients with low-grade oligodendroglioma underwent observant management. With a significant median follow-up period, despite disease recurrence for most patients in this cohort, all but one patient remained alive at the time of last follow-up. These results are similar to those for adult low-grade oligodendroglioma, and again raise the question regarding the optimal timing for RT.[15,33]

Among all patients with low-grade glioma, 25 patients experienced disease recurrence/progression with nine documented progression to high-grade histology. Time-to-progression to high-grade histology for astrocytic tumors was shorter compared to oligodendrogliomas, as expected. Despite radiation therapy at recurrence, these patients exhibited more aggressive tumor behavior with shorter PFS and OS. Our data suggest that while upfront observation after maximal safe surgical resection may be a reasonable radiation-delaying treatment approach for younger patients with *IDH1/2*-mutant LGGs, these patients, especially those with diffuse astrocytomas, should

be monitored closely for disease progression and radiation therapy considered at first relapse to ideally delay progression to higher grade.

Extent of resection significantly affected neither disease progression nor OS of either low-grade histologic type, although there was a trend towards longer survival among patients with low-grade diffuse astrocytoma with better extent of resection. This is in contrast to the adult experience which has generally shown a positive correlation between extent of resection and overall outcome.[34–37] This discrepancy likely reflects the relatively small sample size. Additionally, given the limited use of chemotherapy, we were unable to evaluate its effectiveness within this pediatric cohort. Notably, the proportion of pediatric MGMT-methylated gliomas is unclear, as routine MGMT testing has not been universally adopted.

Genomic characteristics of our pediatric *IDH1/2*-mutant glioma cohort mirrored those of adult *IDH1/2*-mutant gliomas, consistent with the current categorization of these tumors as "adult type" diffuse gliomas in the WHO classification.[7] Of note, a limitation of our retrospective study is that *TERT* promoter mutations may be missed by the NGS panels used for clinical sequencing. Despite the relatively modest patient sample size, several genetic alterations were associated with shorter OS, including *CDKN2A/B*, validating previously reported findings.[38,39] Among *IDH1/2* mutant astrocytomas, *MSH2/6* alterations were associated with poorer OS. While germline testing results were not evaluated in this study, it is possible that these tumors represent mismatch-repair deficiency-associated IDH-mutant gliomas, which have been recently reported to have more aggressive biologic behavior than other IDH-mutant gliomas.[40] Validating our findings within a larger pediatric cohort will provide critical insight into risk stratification and treatment options. Additionally, it will be important to evaluate the safety and efficacy of emerging targeted therapies such as *IDH1/2* inhibitors in pediatrics, as currently underway in the phase 2 subprotocol with ivosidenib in the NCI-COG Pediatric MATCH trial (APEC1621K).[41,42]

Conclusion

We systematically evaluated the frequency of IDH-mutant glioma within the pediatric population and found *IDH1/2* mutations in over 16% of gliomas among patients 10–21 years old. These findings validate previously published data and support the routine testing for *IDH1/2* mutations in all pediatric diffuse gliomas, especially among adolescents. Our data summarizes the pediatric experience with these tumors across several sites and highlights current therapeutic approaches in these United States pediatric institutions. Our clinical experience suggests that there may be a subset of patients with low-grade histology that can be managed observantly, especially if there is an excellent degree of surgical resection. However, long-term outcomes data shows that the clinical behavior of pediatric *IDH1/2*-mutant gliomas is similar to that of adults. This finding affirms the observation that pediatric IDH1/2-mutant low-grade glioma are biologically and clinically distinct from MAPK-activated pediatric low-grade gliomas. Importantly, like their adult counterparts, *IDH1/2*-mutant

pediatric gliomas demonstrate eventual progression to higher histologic grade and corresponding poor clinical prognosis. This suggests a potential role for incorporation of adult treatment approaches including more aggressive therapy, especially at disease recurrence.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology* online.

Keywords

frequency | glioma | IDH1/2 mutation | outcomes | pediatrics

Conflict of interest statement. ELD discloses paid advisory board membership with Day One Biopharmaceuticals and Springworks Therapeutics, both outside the submitted work.

Authorship statement. Experimental Design: KKY, KDW, SA, JAC, JV, KLL. Implementation: KKY, SA, JAC, MML, KK, JV, MM, AS, DA, TJM, SG, MDW, KJN, AT, AC, KLL, KC, AM, MAK. Analysis: KKY, VB, WLB, MLF, JV, SA, JAC, HG. Interpretation of the data: All Authors. Writing of manuscript: All authors.

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