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cIMPACT-NOW Update 3: Recommended diagnostic criteria for “Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV”

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Introduction

The World Health Organization (WHO) central nervous system tumor classification represents the primary source of updates on diagnostic classes, grades and criteria [17]. However, recent and ongoing advances in our understanding of brain tumor molecular pathogenesis warrant more rapid integration of this information into clinical practice between WHO updates. To accomplish this, cIMPACT-NOW (the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy) was established in 2016 [15, 16]. Since then, cIMPACT-NOW has convened three separate working committees to address classification and grading questions and challenges. Working Committee 1 focused on a concern that the classification and grading of Isocitrate Dehydrogenase (IDH)-wildtype diffuse astrocytic gliomas do not reflect our current understanding of the molecular pathogenesis and clinical outcomes associated with these tumors.

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Numerous high profile publications have documented the distinct genetic alterations and clinical behavior of IDH-mutant and IDH-wildtype diffuse astrocytic gliomas in the adult population [4, 6, 8]. Based on this, the WHO has designated IDH-mutant and IDH-wildtype diffuse astrocytic gliomas as distinct diagnostic categories within the 2016 update of the 4th edition [17, 19]. The WHO also recognizes H3 K27-mutant diffuse midline glioma as a tumor with aggressive clinical behavior corresponding to WHO grade IV [19]. Similarly, detection of an H3 G34 mutation in a diffuse glioma, irrespective of histological grade, indicates high grade biology with only modestly longer survivals than other IDH-wildtype glioblastomas [13, 28]. The WHO 2016 does not currently provide a separate classification or grade for H3 G34-mutant diffuse glioma. While these H3 K27- and H3 G34-mutant diffuse gliomas that occur predominantly in childhood and adolescence do not contain IDH mutations, they should not be lumped together with other IDH-wildtype astrocytic gliomas since they have another disease-defining molecular alteration that is associated with an aggressive clinical course. For the remaining IDH-wildtype category, the WHO recognizes diffuse astrocytoma, WHO grade II, and anaplastic astrocytoma, WHO grade III, as provisional entities, and glioblastoma, WHO grade IV. The current criteria for establishing these diagnoses and grades have been based on traditional morphologic findings, with mitotic activity and anaplastic nuclear features distinguishing WHO grade III from WHO grade II, and with the addition of microvascular proliferation and/or necrosis defining WHO grade IV.

Multiple studies have concluded that a substantial subset of IDH-wildtype diffuse or anaplastic astrocytomas that occur in adults and would be considered as WHO grade II or III based on histologic criteria (no microvascular proliferation or necrosis) have an aggressive clinical course, with overall patient survival times equal to or only slightly longer than patients with IDH-wildtype glioblastoma, WHO grade IV [4, 8, 9, 32, 34]. Nevertheless, biologically more favorable glial and glioneuronal tumors, such as ganglioglioma, pilocytic astrocytoma, pleomorphic xanthoastrocytoma, pediatric low-grade diffuse gliomas, and others are also IDH-wildtype and sometimes enter into the differential diagnosis. As such, the lack of IDH mutation alone is thus insufficient for designating a glioma as WHO grade IV. The identification of molecular markers in diffuse astrocytic gliomas that predict a clinical course corresponding to WHO grade IV, regardless of histologic grade, would be welcomed.

Recommended grading parameters: *EGFR* amplification, combined +7/-10 or *TERT* promoter mutation

We evaluated the literature to determine whether there is sufficient evidence to define a minimal set of molecular genetic criteria that could reliably identify IDH-wildtype diffuse or anaplastic astrocytomas that would behave most aggressively, similarly to glioblastoma and thus with a clinical course corresponding to WHO grade IV. Among the molecular features initially considered were: *EGFR* amplification; losses of chromosome 10 (whole chromosome, 10p or 10q); gains of chromosome 7 (whole chromosome, 7p or 7q); *TERT* promoter mutations; homozygous deletion of *CDKN2A/B*; and large-scale, microarray-based DNA methylation profiling. To discuss these possible markers, cIMPACT-NOW

assembled a group of experienced tumor neuropathologists and clinical neuro-oncologists as Working Committee 1, which held three teleconferences in an open manner similar to the discussions held at WHO consensus meetings.

Since clinical management could be substantially altered by the use of such markers for grading, we agreed to consider only those genetic events that were highly specific for aggressive clinical behavior of IDH-wildtype diffuse astrocytic gliomas. We were cautious in our interpretation of the literature, since most large studies on the relationship between genetic alterations and clinical outcomes have relied on retrospective cohorts in which patients were treated differently depending on institution, era and histologic classification. Moreover, we were cautious in our endorsements of markers because we envisioned that some diagnoses would likely be rendered by general pathologists who may be less familiar with brain tumor pathology, brain tumor molecular diagnostics, and the role of integrated diagnoses in current brain tumor diagnosis.

We reached consensus that the following were the minimal molecular criteria for identifying an IDH-wildtype diffuse astrocytic glioma that, despite appearing histologically as a WHO grade II or III neoplasm, would follow an aggressive clinical course more closely resembling that of an IDH-wildtype glioblastoma:

1. *EGFR* amplification
OR
2. Combined whole chromosome 7 gain and whole chromosome 10 loss (+7/−10)
OR
3. *TERT* promoter mutation

These conclusions are based on the findings that those histologic IDH-wildtype diffuse astrocytic gliomas of WHO grade II or III that carry *EGFR* amplification, +7/−10 or *TERT* promoter mutation are associated with significantly shorter patient survival compared to patients with other WHO grade II or III gliomas, and patients have outcomes similar to patients with IDH-wildtype glioblastoma [1, 2, 11, 26, 27, 32, 33]. The large majority of IDH-wildtype diffuse astrocytic gliomas of WHO grade II or III with these genetic signatures correspond histologically to anaplastic astrocytoma, WHO grade III. For example, in the TCGA dataset of over 500 WHO grade II or III diffuse gliomas, there were only six IDH-wildtype diffuse astrocytomas, WHO grade II that had *EGFR* amplification, +7/−10 or *TERT* promoter mutation [6]. In this small subset, clinical outcomes were similar to IDH-wildtype glioblastoma [6]. *EGFR* amplification has excellent specificity for gliomas with aggressive behavior, and is not present in other glioma subtypes that display a more indolent clinical course [27]. Of note, *EGFR* amplification refers to focal high-level copy number gains of the *EGFR* gene, as defined by validated techniques in clinical use. Low-level *EGFR* copy number gains, e.g. trisomy 7, are not sufficient to qualify a tumor as *EGFR*-amplified. Immunohistochemistry for *EGFR* protein does not provide adequate specificity for detecting *EGFR* amplification and should not be used to direct clinical care in this setting [14].

The +7/-10 signature also has excellent specificity, with the rare exception of PXAs, where additional testing (e.g. *BRAFV600E*) may be warranted in diagnostically challenging cases [27]. Some studies have reported on gains of 7p or 7q, as well as losses of 10p or 10q as chromosomal imbalances linked to poor survival for patients with WHO grade II or III IDH-wildtype astrocytic gliomas [2, 27, 29, 32, 33]. However, most studies reported whole gains of chromosome 7 and whole losses of chromosome 10 (+7/-10), and the prognostic association of other, far less common imbalances, such as +7q/-10q, +7/-10q or +7q/-10, was not evaluated separately from +7/-10. A recent investigation by Stichel et al demonstrated that the signatures of +7q/-10 and +7/-10q were each present in approximately 10% of histologic grade II/III IDH-wildtype diffuse astrocytic gliomas and were associated with an adverse prognosis similar to the +7/-10 signature. The +7q/-10 and +7/-10q signatures also demonstrated high specificity for aggressive behavior among IDH-wildtype astrocytic gliomas in that study[27]. Due to the small size of the +7q/-10 (n=12) and +7/-10q (n=9) cohorts and the need for validation, the working group decided to restrict their recommendations primarily to the most common chromosomal imbalances in IDH-wildtype glioblastoma, i.e. +7/-10, as an indicator of WHO grade IV behavior in IDH-wildtype diffuse or anaplastic astrocytomas.

TERT promoter mutations are frequent in IDH-wildtype glioblastoma and aggressively behaving WHO grade II or III astrocytic gliomas. They occur most commonly in IDH-wildtype gliomas with +7/-10 or *EGFR* amplification, yet these markers do not have complete overlap. *TERT* promoter mutations are associated with aggressive clinical behavior, even in some cases without +7/-10 or *EGFR* amplification [2, 8, 32, 33]. Therefore, if the clinical, radiologic and histopathologic features are definitive for a diffusely infiltrative astrocytic glioma, *TERT* promoter mutations can be considered as a marker for WHO grade IV behavior. However, it should be emphasized that other types of IDH-wildtype glial neoplasms without WHO grade IV histology or aggressive behavior have also been reported to occasionally harbor *TERT* promoter mutations, including tumors classified as pleomorphic xanthoastrocytoma, ganglioglioma, anaplastic glioma with piloid features, and ependymoma [12, 25, 27, 31]. In addition, almost all oligodendrogliomas have *TERT* promoter mutations, and therefore this diagnostic consideration should be ruled out by testing for IDH mutations and 1p/19q codeletion. Although these entities can usually be distinguished from a diffuse astrocytic glioma based on morphology, this could be challenging in some instances, especially in a small biopsy. It is therefore critical to establish that a CNS neoplasm is diffusely infiltrative, has astrocytic lineage, and does not contain IDH mutations before applying *TERT* promoter mutation as marker of WHO grade IV behavior of IDH-wildtype gliomas. The combination of *TERT* promoter mutation with other markers, such as *EGFR* amplification and +7/-10 adds specificity as a marker of grade IV behavior [27]. The finding of prognostic interaction of *TERT* promoter mutations with *MGMT* promoter methylation in patients with IDH-wildtype glioblastoma treated with radiochemotherapy with temozolomide warrants further study [3, 21].

Other possible grading parameters

Homozygous *CDKN2A/B* deletions occur with high frequency in aggressively behaving IDH-wildtype diffuse astrocytic gliomas with *EGFR* amplification, +7/-10 or *TERT* promoter

mutation. However, other types of glioma also harbor *CDKN2A/B* deletions, but do not have histologic properties, genetic findings or clinical behavior associated with canonical IDH-wildtype glioblastoma. For example, pleomorphic xanthoastrocytomas often harbor a combination of *BRAF* mutations and *CDKN2A/B* deletions but are associated with substantially better clinical outcomes than IDH-wildtype glioblastoma [30]. Another subset of IDH-wildtype astrocytic gliomas has recently been delineated as anaplastic astrocytoma with piloid features, characterized by frequent *CDKN2A/B* deletions and typically accompanied by *BRAF* pathway gene alterations and *ATRX* mutation or loss of nuclear expression. The respective patients have a more favorable clinical outcome than patients with IDH-wildtype glioblastoma[25]. Therefore, by itself, *CDKN2A/B* deletion is not sufficient as a marker for WHO grade IV behavior in an IDH-wildtype astrocytic glioma.

Whole genome DNA methylation profiling represents a robust and reproducible method for precisely segregating tumor types that have similar histogenesis, genetic signatures and clinical behaviors [5, 6]. IDH-wildtype diffuse astrocytic gliomas of WHO grade II or III with genetic features suggesting aggressive clinical behavior (*EGFR* amplification, +7/–10, *TERT* promoter mutation) have been shown to cluster tightly with IDH-wildtype glioblastoma based on DNA methylation profiling[6, 10, 26]. Other forms of gliomas with indolent clinical features do not cluster together with these tumors, indicating a high degree of specificity for this signature[5]. While the literature indicates this method is superior for classification purposes and could have a role in grading, it currently lacks widespread clinical implementation due to regulatory challenges and prevailing practice patterns that test primarily for mutations and copy number alterations, as well as a reluctance due to uncertainties in reimbursement. Where available, DNA methylation profiling may be an attractive alternative for identifying IDH-wildtype diffuse astrocytic gliomas histologically corresponding to WHO grade II or III that have molecular profiles and clinical behavior of IDH-wildtype glioblastoma, WHO grade IV.

The most recent WHO classification stresses the importance of an integrated diagnosis that incorporates histologic classification, molecular genetic findings and WHO grade [17-19]. Because much of the data discussed above was not mature in 2014 and 2015, the Haarlem and WHO meetings concluded that grading be based on *histological* parameters for the 2016 WHO update [17-19]. The current data, however, show a clear disconnect between histological appearance and clinical behavior; histologically defined WHO grade II or III IDH-wildtype diffuse or anaplastic astrocytomas with *EGFR* amplification, +7/–10 or *TERT* promoter mutation behave clinically as WHO grade IV neoplasms. Since grade is intended to predict clinical behavior, an integrated histological and molecular grade (see Table 1) should take precedence over a strictly histological grade in this instance. In addition, histologic features can be spatially variable within a given tumor, resulting in the potential for undersampling and leading to a histologic diagnosis that underrepresents a tumor's malignant potential. The key genomic alterations described above, on the other hand, appear to be more spatially uniform, potentially resulting in a lower likelihood of molecular undersampling, even when the tissue sample is small.

Diffuse astrocytic glioma, IDH-wildtype with molecular features of glioblastoma, WHO grade IV

With regard to the most appropriate classification, based on genetic similarity and comparable clinical course, it could be argued that these tumors are most appropriately classified as *glioblastoma, IDH-wildtype*, despite not meeting the formal histological criteria. However, there has been reluctance to designate a tumor as a *glioblastoma* in the absence of histological features of glioblastoma and major changes in brain tumor classes and ICD-O codes are best considered as part of the official WHO classification [20]. We therefore reached consensus on the designation *diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV* as the most appropriate terminology at this time, since this conveys the histologic, molecular and clinical features of glioblastoma, but does not alter the long-standing histologic definition. Nonetheless, it is expected that diagnoses will be rendered in a layered format since, by doing so, a diagnosis can clearly show all of the histological and molecular features of any particular lesion (see Table 1).

The diagnosis of *diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma*, together with the designation of integrated WHO grade IV based on molecular parameters, has inherent clinical implications. It will support the current practice of recommending combined chemo- and radiotherapy to patients with IDH-wildtype anaplastic astrocytoma and, potentially, IDH-wildtype diffuse astrocytoma if these have *EGFR* amplification, +7/-10 or *TERT* promoter mutation. For clinical trials, these changes will extend inclusion criteria to allow such patients access to innovative treatments based on their individual risk profile rather than histological diagnosis alone. These clinical trials will ultimately also allow validation of our recommendations in prospective datasets.

Caveats

Importantly, not all IDH-wildtype diffuse or anaplastic astrocytomas have genetic features or clinical outcomes similar to IDH-wildtype glioblastoma. As mentioned above, H3 K27- and H3 G34-mutant diffuse gliomas that occur most often in childhood, adolescence and young adulthood, have clinical and genetic features distinct from IDH-wildtype glioblastoma. Other less common gliomas that occur predominantly in younger patients also lack IDH mutations, but do not have the prototypic genetic alterations of IDH-wildtype glioblastoma, such as *EGFR* amplification, +7/-10, *TERT* promoter, *PTEN*, or *TP53* mutations, or *CDKN2A/B* homozygous deletions. One group has distinct methylation and gene expression profiles and harbors activating *BRAFV600E* mutations, but few other concurrent mutations and copy number alterations [6, 7]. Additional studies are needed on clinical outcomes, yet these patients appear to have a favorable prognosis and some may be responsive to targeted therapies. Also deserving of further study are a small group of IDH-wildtype diffuse astrocytic gliomas that harbor *MYB/MYBL* alterations [1, 24]. Tumors with this single driver genetic alteration occur predominantly in childhood, but have also been described in adults, and have a more indolent clinical course. Thus, the lack of IDH mutation in a diffuse astrocytic glioma, including the examples provided here, does not always equate with

aggressive clinical behavior, highlighting the importance of documenting additional disease-defining genetic events to guide clinical care.

In addition, most studies that relate genetic signatures to clinical outcomes for IDH-wildtype diffuse astrocytic gliomas have been performed on tumors arising in the supratentorial compartment of adults. Signatures predictive of aggressive clinical behavior will not apply to most pediatric diffuse gliomas and may not be relevant to diffuse gliomas arising in other less common sites. For example, IDH-wildtype diffuse astrocytic gliomas that arise in the cerebellum of adults are rare, and recent studies indicate that they do not harbor the same percentage of *EGFR* amplification, +7/–10, or *TERT* promoter mutations as their supratentorial counterparts[22, 23]. A subset will harbor H3 K27 or *SETD2* mutations, but the full spectrum of their other alterations have not been defined, nor have the genetic events corresponding to aggressive behavior. Thus, the genetic signature that predicts poor clinical outcomes for histologic grade II/III IDH-wildtype diffuse astrocytic gliomas of the cerebellum may not be similar to those of supratentorial tumors.

Summary

Working Committee 1 concluded that histologic grade II and III IDH-wildtype diffuse astrocytic gliomas that contain high-level *EGFR* amplification, the combination of whole chromosome 7 gain and whole chromosome 10 loss (+7/–10), or *TERT* promoter mutations, correspond to WHO grade IV and should be referred to as *diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV*. Assessment of classification by DNA methylation profiling and additional +7/–10 signatures appear to be promising as well and could be considered in the future following additional experience and validation. We also concluded that specific molecular signatures in subsets of IDH-wildtype diffuse astrocytic gliomas are associated with better clinical outcomes and should not lead to a high-grade designation, including, but not limited to, those gliomas with *MYB/MYBL* or *BRAF* alterations as individual drivers.

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References

1. Aibaidula A, Chan AK, Shi Z, Li Y, Zhang R, Yang Ret al (2017) Adult IDH wild-type lower-grade gliomas should be further stratified. *Neuro Oncol* 19: 1327–1337 Doi 10.1093/neuonc/nox078 [PubMed: 28575485]
2. Aoki K, Nakamura H, Suzuki H, Matsuo K, Kataoka K, Shimamura Tet al. (2018) Prognostic relevance of genetic alterations in diffuse lower-grade gliomas. *Neuro Oncol* 20: 66–77 Doi 10.1093/neuonc/nox132 [PubMed: 29016839]
3. Arita H, Yamasaki K, Matsushita Y, Nakamura T, Shimokawa A, Takami Het al. (2016) A combination of *TERT* promoter mutation and *MGMT* methylation status predicts clinically relevant subgroups of newly diagnosed glioblastomas. *Acta Neuropathol Commun* 4: 79 Doi 10.1186/s40478-016-0351-2 [PubMed: 27503138]

4. Cancer Genome Atlas Research N, Brat DJ, Verhaak RG, Aldape KD, Yung WK, Salama SR et al. (2015) Comprehensive, Integrative Genomic Analysis of Diffuse Lower-Grade Gliomas. *N Engl J Med* 372: 2481–2498 Doi 10.1056/NEJMoa1402121 [PubMed: 26061751]
5. Capper D, Jones DTW, Sill M, Hovestadt V, Schrimpf D, Sturm Det al. (2018) DNA methylation-based classification of central nervous system tumours. *Nature* 555: 469–474 Doi 10.1038/nature26000 [PubMed: 29539639]
6. Ceccarelli M, Barthel FP, Malta TM, Sabedot TS, Salama SR, Murray BA et al. (2016) Molecular Profiling Reveals Biologically Discrete Subsets and Pathways of Progression in Diffuse Glioma. *Cell* 164: 550–563 Doi 10.1016/j.cell.2015.12.028 [PubMed: 26824661]
7. Chi AS, Batchelor TT, Yang D, Dias-Santagata D, Borger DR, Ellisen LW et al. (2013) BRAF V600E mutation identifies a subset of low-grade diffusely infiltrating gliomas in adults. *J Clin Oncol* 31: e233–236 Doi 10.1200/JCO.2012.46.0220 [PubMed: 23547069]
8. Eckel-Passow JE, Lachance DH, Molinaro AM, Walsh KM, Decker PA, Sicotte Het al. (2015) Glioma Groups Based on 1p/19q, IDH, and TERT Promoter Mutations in Tumors. *N Engl J Med* 372: 2499–2508 Doi 10.1056/NEJMoa1407279 [PubMed: 26061753]
9. Hartmann C, Hentschel B, Wick W, Capper D, Felsberg J, Simon Met al. (2010) Patients with IDH1 wild type anaplastic astrocytomas exhibit worse prognosis than IDH1-mutated glioblastomas, and IDH1 mutation status accounts for the unfavorable prognostic effect of higher age: implications for classification of gliomas. *Acta Neuropathol* 120: 707–718 Doi 10.1007/s00401-010-0781-z [PubMed: 21088844]
10. Hasselblatt M, Jaber M, Reuss D, Grauer O, Bibo A, Terwey Set al. (2018) Diffuse Astrocytoma, IDH-Wildtype: A Dissolving Diagnosis *J Neuropathol Exp Neurol* 77: 422–425 Doi 10.1093/jnen/nly012 [PubMed: 29444314]
11. Hirose Y, Sasaki H, Abe M, Hattori N, Adachi K, Nishiyama Yet al. (2013) Subgrouping of gliomas on the basis of genetic profiles. *Brain Tumor Pathol* 30: 203–208 Doi 10.1007/s10014-013-0148-y [PubMed: 23604523]
12. Koelsche C, Sahm F, Capper D, Reuss D, Sturm D, Jones DT et al. (2013) Distribution of TERT promoter mutations in pediatric and adult tumors of the nervous system. *Acta Neuropathol* 126: 907–915 Doi 10.1007/s00401-013-1195-5 [PubMed: 24154961]
13. Korshunov A, Capper D, Reuss D, Schrimpf D, Ryzhova M, Hovestadt Vet al. (2016) Histologically distinct neuroepithelial tumors with histone 3 G34 mutation are molecularly similar and comprise a single nosologic entity. *Acta Neuropathol* 131: 137–146 Doi 10.1007/s00401-015-1493-1 [PubMed: 26482474]
14. Lee M, Kang SY, Suh YL (2018) Genetic Alterations of Epidermal Growth Factor Receptor in Glioblastoma: The Usefulness of Immunohistochemistry. *Appl Immunohistochem Mol Morphol*: Doi 10.1097/PAI.0000000000000669
15. Louis DN, Aldape K, Brat DJ, Capper D, Ellison DW, Hawkins Cet al. (2017) Announcing cIMPACT-NOW: the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy. *Acta Neuropathol* 133: 1–3 Doi 10.1007/s00401-016-1646-x [PubMed: 27909809]
16. Louis DN, Aldape K, Brat DJ, Capper D, Ellison DW, Hawkins Cet al. (2017) cIMPACT-NOW (the consortium to inform molecular and practical approaches to CNS tumor taxonomy): a new initiative in advancing nervous system tumor classification. *Brain Pathol* 27: 851–852 Doi 10.1111/bpa.12457 [PubMed: 27997995]
17. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (2016) WHO Classification of Tumours of the Central Nervous System. Intl. Agency for Research, City
18. Louis DN, Perry A, Burger P, Ellison DW, Reifenberger G, von Deimling A et al. (2014) International Society Of Neuropathology--Haarlem consensus guidelines for nervous system tumor classification and grading. *Brain Pathol* 24: 429–435 Doi 10.1111/bpa.12171 [PubMed: 24990071]
19. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK et al. (2016) The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol* 131: 803–820 Doi 10.1007/s00401-016-1545-1 [PubMed: 27157931]

20. Louis DN, von Deimling A (2017) Grading of diffuse astrocytic gliomas: Broders, Kernohan, Zulch, the WHO... and Shakespeare. *Acta Neuropathol* 134: 517–520 Doi 10.1007/s00401-017-1765-z [PubMed: 28801693]
21. Nguyen HN, Lie A, Li T, Chowdhury R, Liu F, Ozer Bet al. (2017) Human TERT promoter mutation enables survival advantage from MGMT promoter methylation in IDH1 wild-type primary glioblastoma treated by standard chemoradiotherapy. *Neuro Oncol* 19: 394–404 Doi 10.1093/neuonc/now189 [PubMed: 27571882]
22. Nomura M, Mukasa A, Nagae G, Yamamoto S, Tatsuno K, Ueda Het al. (2017) Distinct molecular profile of diffuse cerebellar gliomas. *Acta Neuropathol* 134: 941–956 Doi 10.1007/s00401-017-1771-1 [PubMed: 28852847]
23. Picart T, Barritault M, Berthillier J, Meyronet D, Vasiljevic A, Frappaz Det al. (2018) Characteristics of cerebellar glioblastomas in adults. *J Neurooncol* 136: 555–563 Doi 10.1007/s11060-017-2682-7 [PubMed: 29196927]
24. Qaddoumi I, Orisme W, Wen J, Santiago T, Gupta K, Dalton JDet al. (2016) Genetic alterations in uncommon low-grade neuroepithelial tumors: BRAF, FGFR1, and MYB mutations occur at high frequency and align with morphology. *Acta Neuropathol* 131: 833–845 Doi 10.1007/s00401-016-1539-z [PubMed: 26810070]
25. Reinhardt A, Stichel D, Schrimpf D, Sahn F, Korshunov A, Reuss DEet al. (2018) Anaplastic astrocytoma with piloid features, a novel molecular class of IDH wildtype glioma with recurrent MAPK pathway, CDKN2A/B and ATRX alterations. *Acta Neuropathol* 136: 273–291 Doi 10.1007/s00401-018-1837-8 [PubMed: 29564591]
26. Reuss DE, Kratz A, Sahn F, Capper D, Schrimpf D, Koelsche Cet al. (2015) Adult IDH wild type astrocytomas biologically and clinically resolve into other tumor entities. *Acta Neuropathol* 130: 407–417 Doi 10.1007/s00401-015-1454-8 [PubMed: 26087904]
27. Stichel D, Ebrahimi A, Reuss D, Schrimpf D, Ono T, Shirahata Met al. (2018) Distribution of EGFR amplification, combined 7gain and 10 loss, and TERT promoter mutation in brain tumors and their potential for the reclassification of IDHwt astrocytoma to glioblastoma. *Acta Neuropathol* (in press): Doi 10.1007/s00401-018-1905-0
28. Sturm D, Witt H, Hovestadt V, Khuong-Quang DA, Jones DT, Konermann Cet al. (2012) Hotspot mutations in H3F3A and IDH1 define distinct epigenetic and biological subgroups of glioblastoma. *Cancer Cell* 22: 425–437 Doi 10.1016/j.ccr.2012.08.024 [PubMed: 23079654]
29. Tabouret E, Nguyen AT, Dehais C, Carpentier C, Ducray F, Idbaih Aet al. (2016) Prognostic impact of the 2016 WHO classification of diffuse gliomas in the French POLA cohort. *Acta Neuropathol* 132: 625–634 Doi 10.1007/s00401-016-1611-8 [PubMed: 27573687]
30. Vaubel RA, Caron AA, Yamada S, Decker PA, Eckel Passow JE, Rodriguez FJ et al. (2018) Recurrent copy number alterations in low-grade and anaplastic pleomorphic xanthoastrocytoma with and without BRAF V600E mutation. *Brain Pathol* 28: 172–182 Doi 10.1111/bpa.12495 [PubMed: 28181325]
31. Vinagre J, Almeida A, Populo H, Batista R, Lyra J, Pinto Vet al. (2013) Frequency of TERT promoter mutations in human cancers. *Nat Commun* 4: 2185 Doi 10.1038/ncomms3185 [PubMed: 23887589]
32. Weller M, Weber RG, Willscher E, Riehm V, Hentschel B, Kreuz Met al. (2015) Molecular classification of diffuse cerebral WHO grade II/III gliomas using genome-and transcriptomewide profiling improves stratification of prognostically distinct patient groups. *Acta Neuropathol* 129: 679–693 Doi 10.1007/s00401-015-1409-0 [PubMed: 25783747]
33. Wijnenga MMJ, Dubbink HJ, French PJ, Synhaeve NE, Dinjens WNM, Atmodimedjo PNet al. (2017) Molecular and clinical heterogeneity of adult diffuse low-grade IDH wild-type gliomas: assessment of TERT promoter mutation and chromosome 7 and 10 copy number status allows superior prognostic stratification. *Acta Neuropathol* 134: 957–959 Doi 10.1007/s00401-017-1781-z [PubMed: 29052002]
34. Yan H, Parsons DW, Jin G, McLendon R, Rasheed BA, Yuan Wet al. (2009) IDH1 and IDH2 mutations in gliomas. *N Engl J Med* 360: 765–773 Doi 10.1056/NEJMoa0808710 [PubMed: 19228619]

Table 1

Sample layered diagnosis and integrated grade for Diffuse astrocytic glioma, IDH-wildtype with molecular features of glioblastoma, WHO grade IV.

Integrated diagnosis: Diffuse astrocytic glioma, IDH-wildtype with molecular features of glioblastoma, WHO grade IV.

Histological diagnosis: Anaplastic astrocytoma

Molecular information:

IDH: wildtype (*IDH1* and *IDH2*, sequencing)

EGFR: High-level amplification (FISH)

Chromosome 7/10 status: whole chromosome 7 gain/ whole chromosome 10 loss (FISH)

TERT promoter: mutated (sequencing)

Integrated histologic and molecular grade: WHO grade IV

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