The 2021 WHO Classification of CNS Tumors: Update of Glial Tumors

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cIMPACT-NOW (Now Officially WHO)
Arabic over Roman numerals in WHO 2021
WHO 5th Edition Nomenclature

- WHO CNS grade 1, 2, 3, or 4
- Grading within types (no more “anaplastic”)
  - Astrocytoma, IDH-mutant (2, 3, or 4)
  - Oligodendroglioma, IDH-mutant and 1p/19q-codeleted (2, 3)
  - (Location) Ependymoma, MPE, SE (1, 2, 3)
- GBM only used for adult IDH-wt tumors
- Grade 4: Molecular GBM, IDH-wt; DMG, H3 K27-alt; DHG, H3 G34-mut; Pedi HGG, IDH- and H3-wt
WHO NOS= Not Otherwise Specified
WHO NEC= Not elsewhere classified
22 New Entities

Diffuse astrocytoma, MYB or MYBL1-altered
Polymorphous low-grade neuroepithelial tumor of the young
Diffuse low-grade glioma, MAPK pathway-altered
Diffuse hemispheric glioma, H3.3 G34-mutant
Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
Infant-type hemispheric glioma
High-grade astrocytoma with piloid features (Methylation only dx)
Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters (provisional entity)
Myxoid glioneuronal tumor
Multinodular and vacuolating neuronal tumor
Supratentorial ependymoma, YAP1 fusion-positive
Posterior fossa ependymoma, PFA
Posterior fossa ependymoma, PFB
Spinal ependymoma, MYCN-amplified
Cribiform neuroepithelial tumor (provisional entity)
CNS neuroblastoma, FOXR2-activated
CNS tumor with BCOR internal tandem duplication
Desmoplastic myxoid tumor, SMARCB1-mutant
Angiomatoid fibrous histiocytoma / Intracranial myxoid mesenchymal tumor
CIC-rearranged sarcoma
Primary intracranial sarcoma, DICER1-mutant
Pituitary blastoma

7 Gliomas
3 Glioneuronal
4 Ependymomas
4 Embryonal
3 Sarcomas
1 Pituitary
Astrocytoma, IDH-mutant
Diffuse midline glioma, H3 K27-altered
Chordoid glioma
Astroblastoma, MN1-altered
Supratentorial ependymoma, C11orf95 fusion-positive
Embryonal tumor with multilayered rosettes
Malignant melanotic nerve sheath tumor
Solitary fibrous tumor
Mesenchymal chondrosarcoma (formerly a subtype)
Adamantinomatous craniopharyngioma (formerly a subtype)
Papillary craniopharyngioma (formerly a subtype)
Pituicytoma, granular cell tumor of the sellar region, and spindle cell oncocyteoma (grouped)
Pituitary adenoma / PitNET
Gliomas

WHO 2016

2.1: Diffuse astrocytic and oligodendrogial tumours

2.1.1: Introduction

2.1.2: Diffuse astrocytoma, IDH-mutant

2.1.3: Diffuse astrocytoma, IDH-wildtype

2.1.4: Diffuse astrocytoma, NOS

2.1.5: Anaplastic astrocytoma, IDH-mutant

2.1.6: Anaplastic astrocytoma, IDH-wildtype

2.1.7: Anaplastic astrocytoma, NOS

2.1.8: Glioblastoma, IDH-wildtype

2.1.8.1: Giant cell glioblastoma

2.1.8.2: Gliosarcoma

2.1.8.3: Epithelioid glioblastoma

2.1.9: Glioblastoma, IDH-mutant

2.1.10: Glioblastoma, NOS

2.1.11: Diffuse midline glioma, H3 K27M mutant

2.2: Oligodendroglia, IDH-mutant and 1p/19q-codeleted

2.2.2: Oligodendroglia, NOS

2.2.3: Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted

2.2.4: Anaplastic oligodendroglioma, NOS

2.2.5: Oligoastrocytoma, NOS

2.2.6: Anaplastic oligoastrocytoma, NOS

2.3: Other astrocytic tumours

2.3.1: Pilocytic astrocytoma

2.3.1.1: Pilocytic astrocytoma

2.3.2: Subependymal giant cell astrocytoma

2.3.3: Pleomorphic xanthoastrocytoma

WHO 2021

2.1: Gliomas, Glioneuronal and Neuronal Tumours

2.1.1: Adult-type diffuse gliomas

2.1.1.1: Astrocytoma, IDH-mutant

2.1.1.2: Oligodendrogioma, IDH-mutant and 1p/19q-codeleted

2.1.1.3: Glioblastoma, IDH-wildtype

2.1.5: Paediatric-type diffuse low-grade gliomas

2.1.5.1: Diffuse astrocytoma, MYB or MYB1-altered

2.1.5.2: Angiocentric glioma

2.1.5.3: Polymorphous low-grade neuroepithelial tumour of the young

2.1.5.4: Diffuse low-grade glioma, MAPK pathway-altered

2.1.2: Paediatric-type diffuse high grade gliomas

2.1.2.1: Diffuse midline glioma, H3 K27-altered

2.1.2.2: Diffuse hemispheric glioma, H3 G34-mutant

2.1.2.3: Diffuse paediatric-type high grade glioma, H3 wildtype and IDH wild type

2.1.3: Circumscribed astrocytic gliomas

2.1.3.1: Pilocytic astrocytoma

2.1.3.2: High-grade astrocytoma with piloid features

2.1.3.3: Pleomorphic xanthoastrocytoma

2.1.4: Glioneuronal and neuronal tumours

2.1.3.7: Ganglioglioma

2.1.3.8: Desmoplastic infantile ganglioglioma / Desmoplastic infantile astrocytoma

2.1.3.10: Dysembryoplastic neuroepithelial tumour

2.2: Diffuse glioneuronal tumour with oligodendroglial-like features and nuclear clusters

2.2.5: Papillary glioneuronal tumour
IDH-mutant Astrocytomas, grades 2-4

Essential diagnostic criteria

- Diffusely infiltrating glioma
  
  AND

- Loss of nuclear ATRX expression or ATRX mutation

  OR

- Exclusion of 1p/19q codeletion

Desirable diagnostic criteria

- TP53 mutation or strong nuclear expression of p53 in > 10% of tumor cells
- Methylation profile of astrocytoma IDH-mutant
- Astrocytic differentiation by morphology
## Grading criteria Astrocytoma, IDH-mutant

<table>
<thead>
<tr>
<th>WHO CNS grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>A diffusely infiltrative astrocytic glioma with an <em>IDH1</em> or <em>IDH2</em> mutation that is well differentiated and lacks histologic features of anaplasia. Mitotic activity is not detected or very low. Microvascular proliferation, necrosis and CDKN2A/B homozygous deletions are absent.</td>
</tr>
<tr>
<td>3</td>
<td>A diffusely infiltrative astrocytic glioma with an <em>IDH1</em> or <em>IDH2</em> mutation that exhibits focal or dispersed anaplasia and displays significant mitotic activity. Microvascular proliferation, necrosis and CDKN2A/B homozygous deletions are absent.</td>
</tr>
<tr>
<td>4</td>
<td>A diffusely infiltrative astrocytic glioma with an <em>IDH1</em> or <em>IDH2</em> mutation that exhibits microvascular proliferation or necrosis or CDKN2A/B homozygous deletion, or any combination of these features.</td>
</tr>
</tbody>
</table>
### IDHm 1p/19q-codel Oligodendroglialomas, grades 2-3

<table>
<thead>
<tr>
<th>Essential diagnostic criteria for oligodendrogloma, IDH-mutant and 1p/19q-codeleted, WHO grade 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>A diffuse glioma</td>
</tr>
<tr>
<td><strong>WITH</strong></td>
</tr>
<tr>
<td>an IDH1 codon 132 or IDH2 codon 172 missense mutation*</td>
</tr>
<tr>
<td><strong>AND</strong></td>
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<tr>
<td>combined whole arm deletions of 1p and 19q</td>
</tr>
<tr>
<td><strong>AND</strong></td>
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<tr>
<td>absence of histological features of anaplasia.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Essential diagnostic criteria for oligodendrogloma, IDH-mutant and 1p/19q-codeleted, WHO grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>A diffuse glioma</td>
</tr>
<tr>
<td><strong>WITH</strong></td>
</tr>
<tr>
<td>an IDH1 codon 132 or IDH2 codon 172 missense mutation*</td>
</tr>
<tr>
<td><strong>AND</strong></td>
</tr>
<tr>
<td>combined whole arm deletions of 1p and 19q</td>
</tr>
<tr>
<td><strong>AND</strong></td>
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<tr>
<td>histological features of anaplasia, including brisk mitotic activity and/or pathological microvascular proliferation with or without necrosis</td>
</tr>
<tr>
<td><strong>AND/OR</strong></td>
</tr>
<tr>
<td>homozgyous CDKN2A deletion**</td>
</tr>
</tbody>
</table>
Glioblastoma, IDH-wildtype, grade 4

Essential and desirable diagnostic criteria

Essential diagnostic criteria:
An IDH-wildtype, H3-wildtype, diffuse astrocytic glioma with one or more of the following:
1. Microvascular proliferation
2. Necrosis
3. TERT promoter mutation
4. EGFR gene amplification
5. +7/-10 chromosome copy number changes

Desirable diagnostic criteria:
An IDH-wildtype, H3-wildtype, diffuse astrocytic glioma with a DNA methylome/molecular profile pattern of glioblastoma, IDH-wildtype
In selected cases, methylation analysis may be helpful.
**IDH-wildtype lower-grade diffuse gliomas: the importance of histological grade and molecular assessment for prognostic stratification**

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**Abstract**

**Background.** Isocitrate dehydrogenase (IDH) wildtype (wt) grade II gliomas are a rare and heterogeneous entity. Survival and prognostic factors are poorly defined.

**Methods.** We searched retrospectively all patients diagnosed with diffuse World Health Organization (WHO) grades II and III gliomas at our center (1989–2020).

**Results.** Out of 512 grade II gliomas, 47 were “diffuse astrocytomas, IDHwt. Tumors frequently had frontal-temporo-insular location (29/42, 62%) and infiltrative behavior. We found bcl2l1a reverse transcriptase (TERT) promoter mutations (23/45, 51%), whole chromosome 7 gains (10/57, 17%), whole chromosome 10 losses (10/41, 24%), and EGFR amplifications (4/43, 9%), but no TERT mutations (0/22, 0%). Median overall survival (OS) was 59 months (vs 70 mo for IDHwt grade III gliomas) (P = 0.0001). Twenty-nine patients (29/45, 67%) met the definition of molecular glioblastoma according to cIMPACT-NOW update 3. Median OS in this subset was 42 months, which was shorter compared with patients with IDHwt grade II gliomas not meeting this definition (median OS: 57 mo), but substantially longer compared with IDHwt grade III gliomas meeting the definition for molecular glioblastoma (median OS: 17 mo, P = 0.0001). Most patients with IDHwt grade II gliomas met cIMPACT criteria because of isolated TERT promoter mutations (16/25, 62%), which were not predictive of poor outcome (median OS: 68 mo). Alternative targets, including 5 gene fusions involving FGFR3, were found in 7 patients (14%).

**Conclusions.** Our findings highlight the importance of histological grading and molecular profiling for the prognostic stratification of IDHwt gliomas and suggest some caution when assigning IDHwt grade II gliomas to molecular glioblastomas, especially those with isolated TERT promoter mutation.
Genetic alterations in uncommon low-grade neuroepithelial tumors: *BRAF*, *FGFR1*, and *MYB* mutations occur at high frequency and align with morphology

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**Table:**

<table>
<thead>
<tr>
<th>Color scale</th>
<th>Genetic alteration</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>Adult-type glioma</td>
</tr>
<tr>
<td>0.3</td>
<td><em>BRAF</em></td>
</tr>
<tr>
<td>1</td>
<td><em>FGFR1</em></td>
</tr>
<tr>
<td></td>
<td><em>MYB/MYBL1</em></td>
</tr>
</tbody>
</table>

**Pathologic Dx**

- AG
- DA
- DNET
- O
- OA
- GG

**Pathologic Gp**

- Astro
- d-OT
- GG

**Anatomic site**

- Frontal lobe
- Occipital lobe
- Parietal lobe
- Temporal lobe

**Age Gp**

- ≤ 3
- > 18
- 4–18

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**Diagram:**

- FGFR1 (Oligo-like)
- MYB/MYBL1 (Diffuse Astro)
- Adult-type glioma

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cIMPACT-NOW update 4: diffuse gliomas characterized by \( MYB, \) \( MYBL1, \) or \( FGFR1 \) alterations or \( BRAF^{V600E} \) mutation

David W. Ellison\(^1 \) - Cynthia Hawkins\(^2 \) - David T. W. Jones\(^3,4 \) - Arzu Onar-Thomas\(^5 \) - Stefan M. Pfister\(^3,6 \) - Guido Reifenberger\(^7 \) - David N. Louis\(^8 \)

**WHO grade 1**

- Diffuse glioma, \( MYB \)-altered;
- Diffuse glioma, \( MYBL1 \)-altered;
- Diffuse glioma, \( FGFR1 \) TKD-duplicated;
- Diffuse glioma, \( FGFR1 \)-mutant;
- Diffuse glioma, \( BRAF \) \( V600E \)-mutant\(^a \);
- Diffuse glioma, other MAPK pathway alteration.
New: “DMG, H3 K27-altered”, WHO grade 4

- Subtype 1: **H3 K27M-mutant** (most common)
- Subtype 2: **EGFR-mutant**
  - Often bithalamic
  - Occasionally with superimposed H3 K27M mutation
- Subtype 3: **H3-wildtype with EZH2IP over-expression**
- Loss of H3K27me3 by IHC in all 3 subtypes
- Most commonly young kids for DIPGs and AYAs for thalamus and spinal cord
- All WHO grade 4 by definition
Diffuse hemispheric glioma, H3 G34-mutant, grade 4
## Ependymomas

<table>
<thead>
<tr>
<th>Location</th>
<th>Age</th>
<th>Sex</th>
<th>WHO grade</th>
<th>Molecular Features</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Supratentorial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST-SE</td>
<td></td>
<td>♂♂♂</td>
<td>1</td>
<td>Balanced genome</td>
<td></td>
</tr>
<tr>
<td>ZFTA</td>
<td>♂♂♂</td>
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<td>1</td>
<td>ZETA fusions, Chromothripsis, CDKN2A/B loss</td>
<td></td>
</tr>
<tr>
<td>ST-YAP1</td>
<td>♂♂♂</td>
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<td>1</td>
<td>YAP1 fusions</td>
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<tr>
<td><strong>Infratentorial</strong></td>
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<td></td>
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<tr>
<td>PF-SE</td>
<td>♂♂♂</td>
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<td>1</td>
<td>Balanced genome</td>
<td></td>
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<tr>
<td>PFA</td>
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<td></td>
<td></td>
<td>EZH2 mutations, H3K27M mutations, Chr. 1q gain</td>
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</tr>
<tr>
<td>PFB</td>
<td>♂♂♂</td>
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<td></td>
<td>Chromosomal instability</td>
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<tr>
<td><strong>Spinal</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SP-SE</td>
<td>♂♂♂</td>
<td></td>
<td>1</td>
<td>Chr. 6q deletion</td>
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</tr>
<tr>
<td>SP-EP</td>
<td>♂♂♂</td>
<td></td>
<td>2 / 3</td>
<td>NF2 mutations</td>
<td></td>
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<tr>
<td>SP-MP</td>
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<td>2</td>
<td>Chromosomal instability</td>
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</tr>
<tr>
<td>SP-MYCN</td>
<td>♂♂♂</td>
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<td></td>
<td>MYCN amplification (Chr. 2p)</td>
<td></td>
</tr>
</tbody>
</table>
Case 1

✓ 36 year-old-man with a brain mass
IDH1
NGS

✓ ATRX p. D1940fs VAF 42%
✓ IDH1 p.R132H VAF 25%
✓ TP53 p.V173L VAF 64%
Diagnosis:
Astrocytoma, IDH-Mutant, WHO CNS grade 3
Case 2:

✓ Young adult with a hemispheric mass
IDH1
ATRX
NGS

✓ CIC p. R1515C VAF 5%
✓ IDH1 p.R132H VAF 38%
✓ TERT c-124 C>T 30%
✓ 1p/19q codeletion
Diagnosis:

- Oligodendroglioma, IDH mutant and 1p/19q codeleted (CNS WHO grade 2)