DIAGNOSTIC CHALLENGES OF BRAIN TUMORS
Molecular Pathology

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DISCLOSURE OF INTEREST

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**WHO Classification of Tumours of the Central Nervous System**

**Histology**
- Astrocytoma
- Oligoastrocytoma
- Oligodendrogloma
- Glioblastoma

**IDH status**
- IDH mutant
- IDH wild-type

**1p/19q and other genetic parameters**
- ATRX loss
- TP53 mutation
- 1p/19q codeletion

- Diffuse astrocytoma, IDH mutant
- Oligodendroglioma, IDH mutant and 1p/19q codeleted
- Glioblastoma, IDH mutant
- Glioblastoma, IDH wild-type

* = characteristic but not required for diagnosis

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After exclusion of other entities:
- Diffuse astrocytoma, IDH wild-type
- Oligodendroglioma, NOS

Genetic testing not done or inconclusive
- Diffuse astrocytoma, NOS
- Oligodendroglioma, NOS
- Oligoastrocytoma, NOS
- Glioblastoma, NOS

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ESMO
The molecular basis of the new WHO classification for gliomas of adulthood
**IDH-1/2 mutation**

Figure 5: Biochemical consequences of glioma-associated isocitrate dehydrogenase (IDH) mutations. Mutated isocitrate dehydrogenase (mIDH) produces less α-ketoglutarate and NADPH, resulting in oxidative stress and methylation abnormalities typical for gliomas, referred to as glioma CpG island methylator phenotype (g-CIMP). Dashed arrow indicates the function of α-ketoglutarate as a co-factor for ten-eleven translocation (TET) and histone demethylases.
1p/19q codeletion

A. von Deimling, Heidelberg

Griffin et al. JNEN 2006;65:988-94
Classification of WHO grade II/III gliomas by comparative genomic hybridization

1. Histology:
   - A3
   - A03
   - O62/O02
   - A0A3/A03

2. MGMT methylation:
   - yes
   - no

3. TERT promoter mutation
   - yes
   - no

4. 1p/19q co-deletion:
   - yes
   - no

5. IDH1/2 mutation:
   - yes
   - no
Diffuse astrocytoma

Definition
A diffusely infiltrating astrocytoma with a mutation in either the IDH1 or IDH2 gene.
Anaplastic astrocytoma

Definition
A diffusely infiltrating astrocytoma with focal or dispersed anaplasia, significant proliferative activity, and a mutation in either the IDH1 or IDH2 gene.
Oligodendroglioma

Definition
A diffusely infiltrating, slow-growing glioma with IDH1 or IDH2 mutation and codeletion of chromosomal arms 1p and 19q

Reference
Anaplastic oligodendroglialoma

Definition
An IDH-mutant and 1p/19q-codeleted oligodendroglialoma with focal or diffuse histological features of anaplasia (in particular, pathological microvascular proliferation and/or brisk mitotic activity)
Glioblastoma

Definition
A high-grade glioma with predominantly astrocytic differentiation; featuring nuclear atypia, cellular pleomorphism (in most cases), mitotic activity, and typically a diffuse growth pattern, as well as microvascular proliferation and/or necrosis; without mutations in the IDH genes.
What is glioblastoma in 2018?

„Molecular“ glioblastoma: the next step?

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

- EGFR amplification
- +7/-10 genotype
- TERT promoter mutation

Diffuse midline glioma

Definition
An infiltrative midline high-grade glioma with predominantly astrocytic differentiation and a K27M mutation in either H3F3A or HIST1H3B/C.
Standardizing the diagnostic approach based on the 2016 WHO classification
THE 2017 EANO GUIDELINE
LANCET ONCOLOGY 2017;18:E315-E329

Diffuse astrocytic or oligodendroglial glioma

**IDH mutant (CIMP+)**
- 1p/18q codeleted (TERTp mutant)
  - WHO grade II
    - Watch & wait
    - RT → PCV (or RT/TMZ → TMZ)
  - WHO grade III
  - Watch & wait
- 1p/18q intact (ATRX mutant, TP53 mutant)
  - WHO grade II
    - Watch & wait
  - WHO grade III
    - Watch & wait
  - WHO grade IV
    - MGMT –

**IDH wild-type (CIMP-)**
- WHO grade III*
  - Watch & wait
  - MGMT –
  - MGMT +
  - < 70 years
    - RT
  - > 70 years
    - RT (or TMZ/RT → TMZ)
- WHO grade IV
  - MGMT –
  - MGMT +
  - RT
  - TMZ/RT → TMZ

**H3-K27M mutant**
- WHO grade IV
  - RT
  - TMZ/RT → TMZ

* Refers to the provisional entities of diffuse astrocytoma, IDH wildtype, and anaplastic astrocytoma, IDH wildtype.
Molecular testing in gliomas: what is standard of care?

- IDH status (immunohistochemistry, sequencing in patients below 55-60 years of age)
- 1p/19q status in IDH-mutant tumors
- MGMT in IDH-wildtype tumors
- BRAFV600E in subsets (epithelioid glioblastoma, pleomorphic xanthoastrocytoma)
- NTRK fusions? FGFR-TACC fusions?
Figure A. Axial T1 MRI with contrast shows no evidence of a brain tumor.

Figure B. Eight months later, a large glioblastoma has developed.

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**Evolution of glioblastoma**

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TECTURE OF TUMOR-DERIVED DNA IN CEREBROSPINAL FLUID OF PATIENTS WITH PRIMARY TUMORS OF THE BRAIN AND SPINAL CORD

Yuxuan Wang1,2, Simon Springer1,2, Ming Zhang3,4, K. Wyatt Middahoni5, Isaac Kinke6, Lisa Doblin5, Janice Pea4, Henry Breen3, Kaborns Chachuma3, Gary L. Godbey7, Zyza L. Sokalski1, Matt L. Grow9, George J. Jull2, Michael Lim2, Alessandro Oli6, Alfredo Quiros-Oropel6, Dariole Rigananto6, Greg J. Riggin2, Daniel M. Sculba6, Jun D. Weninger5, Jean-Rudolf Wolfring4, Xiaohu Ye, Suei Miki Kobo-Shinji6, Suzy K. N. Mase6, Matthias Holdhoff1, Nishant Agrawal1, Luis A. Diaz Jr.1, Nikolas Papadopoulos1, Kenneth W. Kinzie6, Bert Vogelstein1, and Christian Bertaina1,2,4

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Clinical Cancer Research

Molecular diagnosis of diffuse gliomas through sequencing of cell-free circulating tumor DNA from cerebrospinal fluid

Franklin Sample-Koehler, Nicholas D’Souza, Faisal Baharvand, Craig Rode Perez, Carlos Thibado, Christian Cengel, Aimee Cavender, Michael J. Kinne, Samantha R. Benes, Santiago Bastero, Cristian Marques, Joan Carles, Jose M. Palacino, Alexia Plesser, Stefan Geisler, Florian Crone, Joan Guevara, and Joan Sosa.

Cerebrospinal fluid cell-free tumour DNA as a liquid biopsy for primary brain tumours and central nervous system metastases

J. Seoane5,6,7, L. De Mattos-Arruda1, E. Le Rhun8,9,10, A. Bardelli8,9 & M. Welke10

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REVIEW
Improving brain tumor diagnosis beyond the new WHO classification by genomic methylation profiling?

Capper et al. Nature 2018;555:469-474
Improving brain tumor diagnosis beyond the new WHO classification by genomic methylation profiling?

Figure 4 | Reassessment of discrepant cases and establishment of new diagnosis. Discrepancy between pathological diagnosis (left) and methylation profiling (middle) was observed for 139 cases. For 129 cases, histological and molecular reassessment (Supplementary Table 5) resulted in a change in the initial diagnosis with formulation of a new integrated diagnosis (right). For 92 cases, this involved a change in the WHO grading, with both down- (blue) and upgrading (red). Integrated diagnoses in brackets are not recognized as a WHO entity. For methylation class abbreviations see Supplementary Table 1.

Capper et al. Nature 2018;555:469-474