



**Topic:** Molecular Biomarker Testing for the Diagnosis of Diffuse Gliomas

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### Why was this guideline created?

Up until 2016, diffuse gliomas were largely classified based on morphology, with molecular testing playing an ancillary role. However, advances in the field have uncovered molecular genetic alterations that can be used to classify DG into clinically meaningful subsets. The increasing complexity and rapid pace of change in diagnostic criteria, relevant molecular biomarkers, laboratory testing platforms, and clinical practice warranted the development of the “Molecular Biomarker Testing for the Diagnosis of Diffuse Gliomas” guideline.<sup>1</sup>

### Does the guideline align with WHO-defined entities?

This guideline is consistent with the 5<sup>th</sup> edition of the WHO Classification of Tumours of the Central Nervous System.<sup>2</sup> Beginning in 2024, the CAP Center for Evidence-based Guidelines will assess the guideline to try to maintain consistency and to determine if updates are needed.

### Which biomarkers were considered for this guideline? How were they selected?

During initial conference calls, the expert and advisory panel developed a list of genetic mutations/alterations they believed important for the diagnosis of diffuse gliomas. They considered tests needed for WHO-defined entities as well as emerging biomarkers showing promising prognostic utility. The expert panel agreed on the final list prior to the literature search. They ultimately collected data for 20 genetic mutations/alterations. A list can be found in the methods supplement on [cap.org](https://cap.org).

### Which one or two recommendations are most important to implement?

Recommendation 1 is very important clinically, since the identification of DG with IDH mutations is very important for clinical management decisions. Similarly, recommendations 6 and 9 are very important, since the identification of DG that fulfill molecular criteria for glioblastoma, IDH-wildtype is critical to patient management (Recommendation 9), as is the determination of MGMT promoter methylation status in this patient population (Recommendation 6).

Recommendation 1. IDH mutational testing must be performed on all diffuse gliomas.

Recommendation 6. *MGMT* promoter methylation testing should be performed on all glioblastoma (GBM), IDH-wild type (WT).

Recommendation 9. For histologic grade 2-3 DG that are IDH-WT, testing should be performed for whole chromosome 7 gain/whole chromosome 10 loss, *EGFR* amplification, and *TERT* promoter mutation to establish the molecular diagnosis of GBM, IDH-WT, grade 4.

### Are the biomarker testing algorithms provided in the manuscript all encompassing?

No. The algorithms are a visual representation of the molecular tests recommended by the guideline. These tools can help pathologists arrive at a WHO-defined entity and begin with the determination of whether IDH1/2 mutations are present or not. Not every biomarker/mutation/alteration is addressed by the guideline or included in the algorithm. Even among the recommended biomarkers and tests, variation can occur. Laboratories may offer testing in a manner that does not follow the workflow or could decide to perform tests not mentioned in the guideline manuscript. Again, the algorithms are tools to help laboratories implement the guideline recommendations.

### What are “good practice statements” and why aren’t these recommendations?

Good practice statements are defined as statements having a “high level of certainty that the recommendation will do more good than harm (or the reverse), but where there is little direct evidence.”<sup>3,4</sup> A targeted search identified studies and data was extracted for the panel to make a judgment on the use of the biomarkers named in the good practice statements. The studies did not



undergo quality assessment and many of the sample sizes were small. It is likely however, that when the guideline is updated, there may be enough data to make recommendations on these biomarkers in the future.

**How will the guideline be enforced? What happens if a laboratory doesn't follow the guideline?**

As with any clinical evidence-based guideline, following the recommendations is not mandatory. It is only highly encouraged that laboratories adopt these recommendations. Laboratories should follow the requirements of regulatory and/or their accrediting agency.

**REFERENCES**

1. Brat DJ, Aldape K, Bridge JA, et al. Molecular biomarker testing for the diagnosis of diffuse gliomas: Guideline from the College of American Pathologists in collaboration with the American Association of Neuropathologists, Association of Molecular Pathology, and Society for Neuro-Oncology. *Arch Pathol Lab Med*. 2022; 146(5): 547–574. doi:10.5858/arpa.2021-0295-CP.
2. WHO Classification of Tumours Editorial Board. *WHO Classification of Tumours of the Central Nervous System*. International Agency for Research on Cancer; 2021. *World Health Organization Classification of Tumours*, 5<sup>th</sup> ed.; vol 1.
3. Guyatt GH, Alonso-Coello P, Schunemann HJ, et al. Guideline panels should seldom make good practice statements: guidance from the GRADE Working Group. *J Clin Epidemiol*. 2016;80:3-7
4. Tugwell P, Knottnerus JA. When does a good practice statement not justify an Evidence Based Guideline? *J Clin Epidemiol*. 2015;68(5):477-479.