Since the early 1900s, and until the 2016 revised 4th edition of the World Health Organization (WHO) *Classification of Tumours of the Central Nervous System,*[1] DGs were classified based upon the morphologic features of neoplastic cells, with molecular testing playing an ancillary role.

During the past decade, numerous investigations have uncovered molecular genetic alterations that can be used to reliably and reproducibly classify DGs into clinically meaningful subsets, leading the 2016 WHO revised 4th edition update to incorporate diagnostic entities based on the integration of morphologic features with molecular biomarkers.[1–6] More recent advances in our understanding of the pathogenesis and clinical behavior of specific DG subtypes has led to the inclusion of additional molecular biomarkers into clinical practice and the 2021 WHO 5th edition relies even more on molecular test results for diagnosis and grading.[7–11] DNA methylome profiling continues to identify numerous tumor types with specific methylation patterns that have characteristic genetic alterations and clinical behavior.[12] The increasing complexity and rapid pace of change in diagnostic criteria, relevant molecular biomarkers, laboratory testing platforms, and clinical practice warrant the development of evidence-based recommendations on biomarker testing for DGs.

## DESIGN

This evidence-based guideline was developed following the standards endorsed by the National Academy of Medicine.[13] A detailed description of the methods and the systematic review (including the quality assessment and complete analysis of the evidence) used to create this guideline can be found in the supplemental digital content (SDC) at https://meridian.allenpress.com/aplm in the May 2022 table of contents.

## PANEL COMPOSITION

The College of American Pathologists (CAP) in collaboration with the American Association of Neuropathologists, Association for Molecular Pathology, and Society for Neuro-Oncology convened a multidisciplinary expert panel consisting of 13 practicing pathologists from a variety of specialties, institution types, and other professional groups, 2 oncologists who were representatives of the American Society of Clinical Oncology, 1 patient advocate, and a research methodologist consultant to develop this guideline. An advisory panel assisted the expert panel at specific key stages in the development of the guideline. All panel members, except for the methodologist consultant, volunteered their time and were not compensated for their involvement. Detailed information about the panel composition can be found in the SDC.

## CONFLICT OF INTEREST POLICY

The collaborators agreed upon a conflict of interest policy (effective June 2017), and members of the expert panel disclosed all financial interests from 3 years before appointment through the development of the guideline. Individuals were instructed to disclose any relationship that could be interpreted as constituting an actual, potential, or apparent conflict. Complete disclosures of the expert panel members are listed in the Appendix. Disclosures of interest judged by the oversight group to be manageable conflicts are as follows: HC – Consultancies with F. Hoffman-La Roche, Ltd (Basel, Switzerland), Genentech USA, Inc. (South San Francisco, California), Upsher-Smith Laboratories, LLC (Grove, Minnesota), Novocure (St. Helier, Jersey), Insys Therapeutics (Phoenix, Arizona), Mateon Therapeutics (formerly OxiGENE) (Agoura Hills, California), CytRx Corp. (Los Angeles, California), Omniox Inc. (San Carlos, California), AbbVie Inc. (North Chicago, Illinois); EH – Consultancies with E.R. Squibb&Sons, LLC (New Brunswick, New Jersey), Honorarium from Arbor Pharmaceuticals, LLC (Atlanta, Georgia); MvdB – Consultancies with Bristol Myers Squibb (New York, New York), Celldex Therapeutics, Inc. (Hampton, New Jersey), Vaximm AG (Basel, Switzerland), Carthera, Nerviano, Agios, Honorarium from Merk Sharp & Dohme Corp (Kenilworth, New Jersey), Research Grants from AbbVie Inc (North Chicago, Illinois).

Most of the expert panel (14 of 17 members) were assessed as having no relevant conflicts of interest. The CAP provided funding for the administration of the project; no industry funds were used in the development of the guideline. All panel members volunteered their time and were not compensated for their involvement, except for the contracted methodologist. See the SDC for complete information about the conflict of interest policy.

## GUIDELINE OBJECTIVES

The expert panel addressed the overarching question, "What ancillary tests are needed to classify DGs to sufficiently inform the clinical management of patients?" To answer this, several more pointed key questions (KQs) were developed as follows:

KQ 1a: What genetic and molecular alterations should be included for optimal classification of DGs?
KQ1b: What are the acceptable techniques/methods for molecular genetic testing of DGs? What are the expected turnaround times for individual assays?
KQ1c: What are the acceptable techniques/methods for assessing whole genome copy number alterations?
KQ 2: What are the core molecular tests/findings that provide sufficient classifying information in the setting of discrete clinicopathologic entities?
KQ 3: What are the acceptable techniques/methods/criteria for determining *MGMT* promoter methylation status?

## OUTCOMES OF INTEREST

The panel established outcomes of interest for both clinically based and pathology-based studies/articles. The clinical outcomes of interest included survival rates (overall, 1-year and 3-year survival, progression free), recurrence rates, response to treatment, and accuracy of diagnosis. The pathologic outcomes of interest included sensitivity, specificity, positive predictive value, negative predictive value, concordance, turnaround time, reproducibility of the various tests, as well as mutation/alteration/deletion status (percent, presence, frequency, and association with other alterations) for the molecular targets of interest.

The target audience of this review are those within the neuro-oncology community who care for patients with DGs, including pathologists, neuroradiologists, neurosurgeons, radiation oncologists, neuro-oncologists, medical oncologists, and other members of the patient care team. Recommendations will also be highly relevant to brain tumor investigators, epidemiologists, and cancer registrars.