RECENT ADVANCES IN NEUROPATHOLOGY: WHO CNS TUMOR CLASSIFICATION AND MOLECULAR MARKERS

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Abstract
The role of the neuropathologist in the diagnosis of tumours of the CNS is important and has an impact on the care of the patients. The recent changes made in the 2021 World Health Organization (WHO) Classification of CNS Tumors are highlighted with an emphasis on 'inclusive' molecular diagnosis and important molecular markers. Important biomarkers such as IDH, 1p/19q codeletion, EGFR or H3 changes have helped to classify tumors, to view the prognosis and to choose an adequate treatment. Besides, the review emphasizes current molecular diagnostics technologies, precision medicine and AI in the domain of neuropathology. These advances are very useful for making a more accurate diagnosis and treating the patient and give a good basis for future advances in the management of CNS tumors.

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1. Introduction

Neuropathology is the study of diseases of the brain, spinal cord and nervous system. It is very important for the diagnosis of central nervous system (CNS) tumors and directing the selection of the most effective treatment for these tumors. In the old days, CNS tumors were primarily divided based on the microscopic features of the tumor. Tumors, though similar in appearance, may have different genetic mutations and have different activities. For this reason, a contemporary diagnosis will include both molecular testing and histology to see how accurate the diagnosis is. An integrated approach was introduced by the World Health Organization (WHO) Classification of CNS tumors (2021), which serves to enhance the reliability of diagnosis and provides a basis for personalized treatment. This review covers the latest developments in the classification of CNS tumours by the WHO classification and the relevance of molecular markers in the current era of neuropathology.

2. Evolution of WHO CNS Tumor Classification

2.1 From Histology to Integrated Molecular Classification

The earlier WHO classifications grouped **central nervous system** (CNS) tumors primarily by the way the cells within the tumor look under the microscope. While this approach was helpful, it was not always able to account for the variations in tumor behaviour or between patients' outcomes. Later, it was determined that genetic and molecular modification is a big component of the process of tumor formation. This led to the development of molecular taxonomy to increase the accuracy of the diagnosis and minimize misinformation in treatment planning.

2.2 WHO CNS5 (2021): Major Advances

There has been a significant revision in the classification of CNS tumors with the 5th edition of the WHO Classification published in 2021, which started the integration of molecular data into the classification. This integrated diagnosis will help towards the more precise classification of tumours and minimize the discrepancy in diagnosis between labs. A new layering of the system was added with the example of multi-layered reports of histological, molecular and clinical data. The grading system was also changed to make better use of the biological behaviour and prognosis of the tumor.

2.3 cIMPACT-NOW and Ongoing Updates

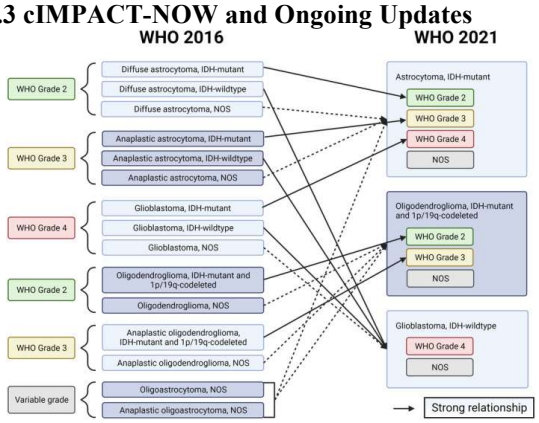

Figure 1. Evolution of WHO CNS Tumor Classification and Integrated Diagnostic Framework
(Source: https://pmc.ncbi.nlm.nih.gov/articles/PMC9245936/figure/bpa13062-fig-0001/)

The Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW) meets regularly to approve the latest scientific evidence to support regular updates in the CNS tumor classification. The recommendations make a contribution between the WHO editions and facilitate more accelerated incorporation of new molecular discoveries into clinical practice, contributing to the diagnosis and treatment of CNS tumors.

2.4 Impact of the WHO CNS5 Classification on Clinical Practice

The WHO CNS5 classification has revolutionized clinical treatment and management of the CNS tumors. The association of these histological analysis results with molecular knowledge will help to more accurately determine tumor subtypes and minimize potential misdiagnosis. This is particularly helpful in cases where there are tumour types with the same microscopic characteristics but diverse genetic signatures. Consequently, the treatment plan will be better matched to the biological nature of the tumor, thereby benefiting patients.

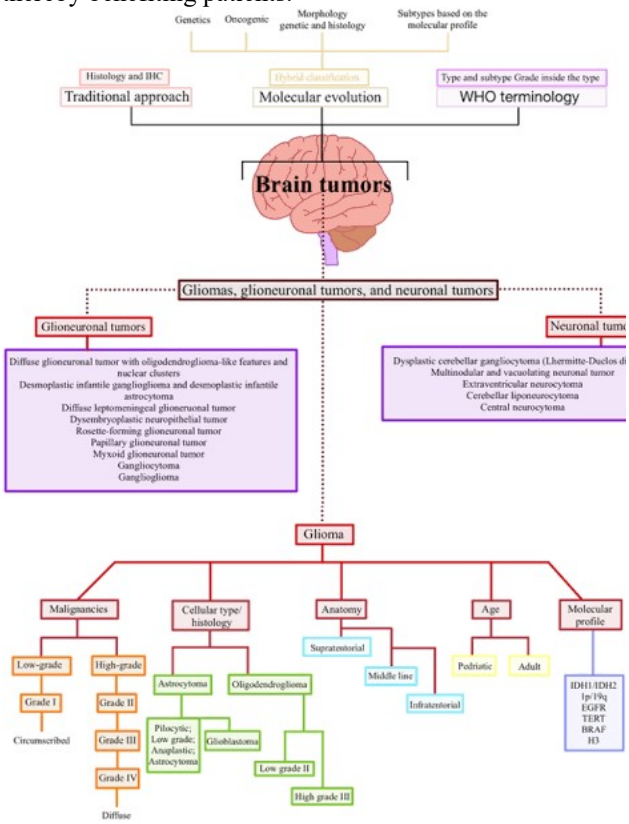

Figure 2. Evolution of WHO CNS tumour classification from traditional histopathology to integrated molecular classification of brain tumours.

(Source: https://link.springer.com/article/10.1007/s10571-025-01642-1)

The new classification is also likely to facilitate the communication between pathologists, radiologists, neurosurgeons and oncologists. Implementing a standardized reporting system will enable all professionals working with the patient to comprehend the diagnosis in the same manner, which will result in treatment being made consistent throughout. Molecular classification also aids in identifying patients that could benefit from targeted therapy or clinical trials. The enhancements help in treating the patient more individually, which can also help in achieving improved outcomes, such as survival and quality of life. With ongoing research, further molecular markers will undoubtedly be added to future classifications and thus enhance the accuracy of the diagnosis and progress towards new treatment strategies for CNS tumors.

3. Molecular Markers Transforming CNS Tumor Diagnosis

3.1 Adult-Type Diffuse Gliomas

The diagnosis of adult type diffuse gliomas has significantly improved with the use of molecular markers. One of the most important markers is IDH mutations which can distinguish good survival from the more aggressive cancers. Oligodendroglioma is characterised by the 1p/19q codeletion which is helpful for tumour classification. Astrocytoma accumulates loss of the ATRX gene, and mutations of the TP53 gene are often detected that distinguish them from other gliomas (Sahm et al., 2023). There are links between EGFR amplification and fast tumor growth as well as TERT promoter mutations and higher survival of tumor cells and low prognosis in the case of glioblastoma. These molecular markers are valuable in terms of providing important information regarding disease behaviour, which can be used to classify tumors with greater precision than is possible by a purely histological diagnosis, and together they contribute to the improvement of diagnostic accuracy (Van der Meulen et al., 2022).

3.2 Pediatric and Other CNS Tumors

Molecular markers can also be important when making a classification of pediatric and other **circular nervous system** (CNS) tumors. The **H3 K27-altered** form of mutations occurs frequently in diffuse midline gliomas and is associated with high grade and dismal prognosis. Another group of paediatric high grade gliomas which have unique biological characteristics are the **H3 G34-mutant tumours**. The **BRAF alterations**, including BRAF V600E mutation are common in certain low-grade pediatric gliomas, and may be amenable to targeted therapy (Bertero et al., 2024). Also, medulloblastomas have been subdivided into molecular groups, such as **WNT, SHH, Group 3 and Group 4**, which display differing genetic characteristics, prognosis and treatment responses.

3.3 Clinical Significance of Molecular Markers

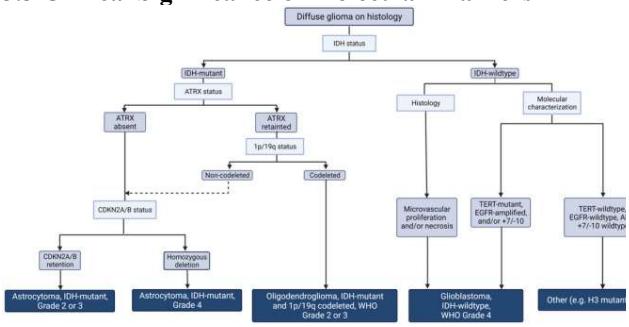

Figure 3. Major Molecular Markers Used in WHO CNS Tumor Classification
(Source: https://pmc.ncbi.nlm.nih.gov/articles/PMC9245936/figure/bpa13062-fig-0007/)

The diagnosis and treatment of CNS tumors has been transformed by molecular markers. They help doctors identify the types of tumors by making them more accurate in their diagnosis. These are also useful for prognosis of the tumor and for determining how strongly the tumour is likely to appear or react to the treatment. Targeted therapies are used to treat patients that match the gene characteristics of their tumour and some biomarkers help indicate their use. This will minimise over-treatment and potentially enhance clinical outcomes (McNamara et al., 2022). Molecular testing can also be used to help personalize medicine by correlating genetic data with clinical and pathological data to establish personalized treatment. With the discovery of more and more biomarkers, molecular profiling will have an even greater influence in improving diagnosis, selecting effective treatments and helping with better long-term management of patients with CNS tumors.

Molecular Marker	Associated CNS Tumor	Clinical Significance
IDH mutation	Astrocytoma, Oligodendroglioma	Helps in the diagnosis and has an improved prognosis.
1p/19q codeletion	Oligodendroglioma	Confirms diagnosis and anticipates good improvement in treatment.
ATRX / TP53	Astrocytoma	Discriminates astrocytoma from other types of gliomas.
EGFR / TERT	Glioblastoma	Correlated to high aggressiveness of the tumours and low prognosis.
H3 K27 / H3 G34	Pediatric diffuse gliomas	Defines certain pediatric tumour subsets and prognosis.
BRAF alteration	Pediatric low-grade gliomas	Facilitates the ability to engage in targeted therapy and personalized treatment.

Table 1. Major Molecular Markers, Associated CNS Tumors, and Clinical Significance

3.4 Emerging Molecular Biomarkers and Their Clinical Potential

Within the last few years, a variety of novel molecular markers have been discovered, which have the potential to contribute further to the diagnosis and disease management of CNS tumors. These biomarkers offer another perspective on the characteristics of the tumor, and could help determine which patients could potentially be most responsive to certain treatments. FGFR gene changes are known to occur in some gliomas and glioneuronal tumors and may thus become targets for new therapies. In the same way, a number of gene fusions are clinically significant as well, though they are rare, and those patients with these gene fusions might respond to the treatment with TRK inhibitors (Torp et al., 2022).

A second key focus of study is DNA profiling by methylation analysis—this is a very useful tool for classification of tumors that are hard to diagnose by traditional histology. Tumors that are very similar to each other microscopically can actually have different methylation patterns which allows the pathologist to better classify the tumor. This has helped to establish a more accurate classification of rare, CNS tumors, as well as aided the elucidation of new tumor types that were previously considered combined (Komori, 2022).

Methods of studying epigenetic changes, RNA expression profile and microRNA biomarkers in CNS tumors are also under investigation. These molecular characteristics could provide further clues as to tumour progression, treatment response and disease recurrence. Many of these biomarkers are under further investigation, but have recently been used in clinically successful studies, and may form a future part of the WHO classification.

The use of comprehensive molecular profiling has also helped to better understand tumour heterogeneity as it grows.As more and more comprehensive molecular profiling is used, tumour heterogeneity becomes increasingly understood. Variations in the genetic alterations affecting the different parts of a tumour may lead to different patient outcomes in the same type of cancer. When multiple molecular markers can be extracted, they can be used to create a more comprehensive profile of every patient's tumor, and the patient will be prescribed a treatment that is tailored to their own unique genetic make-up (d'Amati et al., 2024). This strategy will help further develop precision medicine and will likely develop more favorable long-term responses for individuals with CNS tumors.

4. Molecular Diagnostic Technologies and Clinical Applications

4.1 Modern Diagnostic Technologies

The diagnosis of CNS tumours has become more accurate with modern molecular diagnostic technologies. **Immunohistochemistry** (IHC) is most often utilized for searching out specific proteins which might assist in identifying certain kinds of tumor. **Fluorescence in situ hybridization** (FISH) is used to identify chromosomal changes that are important and **polymerase chain reaction** (PCR) is used to detect specific mutations in genes. **Next-Generation Sequencing** (NGS) offers detailed information about multiple genetic changes in a single test, which makes this tool useful for determining the type of tumour (Mahajan et al., 2022). Diagnosis becomes even better using DNA methylation profiling which is a technique that reveals molecular patterns unique to each diagnosis that can't be detected by normal microscopic methods. These technologies might aid in the more precise and accurate classification of CNS tumors.

4.2 Precision Medicine and AI in Neuropathology

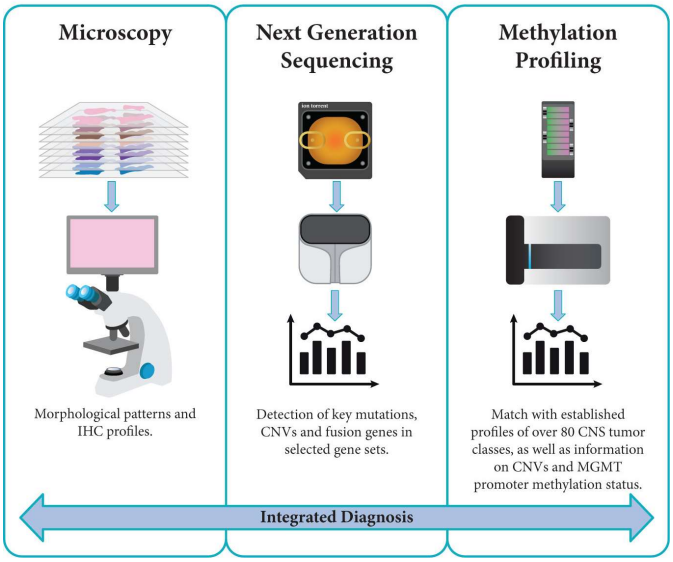

Figure 4. Molecular Diagnostic Workflow in Precision Neuropathology
(Source: https://ars.els-cdn.com/content/image/1-s2.0-S0923753419312839-gr1_lrg.jpg)

Precision medicine takes molecular data to match treatments to the genetic characteristics of a tumor in each patient. A molecular diagnosis that is integrated with histology and clinical characteristics is used to make medical decisions and care for the patient. The power of biomarker guided treatment enables the use of more effective targeted treatment depending on the tumour type (Gritsch et al., 2022). The use of artificial intelligence (AI) is also gaining significance in neuropathology, where AI models are increasingly being used to analyze digital slides and identify tumor patterns, contributing to more accurate diagnoses. With digital neuropathology, image analysis can be completed faster, diagnostic variation can be diminished and pathologist decisions will be more consistent. These advances, in combination, are helping to better diagnose, plan, and provide individualized care to patients with CNS tumors.

Technology	**Clinical Application**
Immunohistochemistry (IHC)	Recognizes protein markers used for the detection of tumors.
FISH	Detects abnormalities in the chromosomes and rearrangement of genes.
PCR	Identifies the presence of specific abnormalities in

	genes that are involved in CNS tumors.
Next-Generation Sequencing (NGS)	Recognises several genomic changes for correct diagnosis of a tumour.
DNA Methylation Profiling	Helps distinguish tumor types and aids to make accurate diagnoses.

Table 2. Molecular Diagnostic Technologies and Their Clinical Applications

4.3 Emerging Diagnostic Approaches and Future Clinical Applications

Recently, new molecular diagnostic technologies have improved the early diagnosis and management of CNS tumours. An important development so far is the discovery of new genetic material in the blood or CSF which is associated with the tumor (Osborn et al., 2022). This technique is less invasive than conventional tissue biopsy and can be performed throughout the treatment to detect early signs of any recurrence of the tumor. Liquid biopsy is still in its infancy for routine clinical use, but it has been a great improvement in patient monitoring.

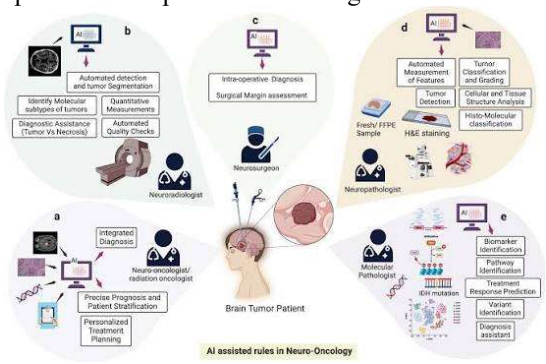

Figure 5: Artificial intelligence-assisted applications in neuro-oncology

(Source: https://www.nature.com/articles/s41698-024-00575-0)

One important development is the use of multi-omics analysis, combining study of the tumor genome, transcriptome, proteome, and epitome, to generate a more complete picture of the biology of tumors. A full-scale approach could lead to elucidation of novel markers leading to improved understanding of the mechanisms of cancer progression and identification of novel targets for therapy. The rapidly evolving technologies of computational environments allow an increasingly large amount of molecular data to be analysed with greatly improved accuracy and timeliness (Halfpenny and Wood, 2023).

New data sharing tools in the cloud and new advanced bioinformatics platforms also are facilitating collaboration between research institutions and hospitals. These technologies enable clinicians to cross-reference the molecular results to an international database, helping to increase consistency in diagnosis and improvement of recommendations for treatment. Future incorporation of molecular diagnostics with the use of artificial intelligence and advanced imaging will further improve diagnostic accuracy, provide support for personalized treatment decision making in patients with CNS tumors and overall patient management.

5. Clinical Impact of Molecular Neuropathology

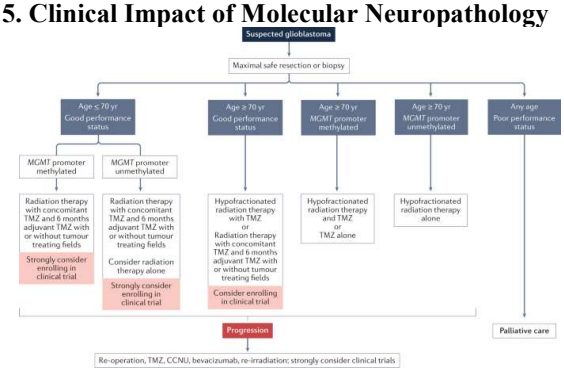

Figure 6: Molecular marker (MGMT promoter methylation)-guided clinical management algorithm for suspected glioblastoma

(Source: https://www.nature.com/articles/s41582-022-00679-w)

Molecular neuropathology has greatly improved the clinical management of central nervous system (CNS) tumors by supporting more accurate diagnosis and personalized treatment. The diagnosis can consist of both histopathological results and molecular tests and help to determine both tumor type and the biological behavior (Chai et al., 2022). This aids in minimizing diagnostic uncertainty and optimizing the management of patients in treatment. Other molecular markers also yield valuable prognostic data useful to tailoring the most fit clinical therapy, as they are able to detect tumors with a more or less aggressive nature (Guo et al., 2023). In addition, molecular profiling enables the use of targeted therapies – where therapies are tailored to the molecular characteristics of the tumour, to match them to the patient. This can help to get more out of treatment and minimize adverse effects that are not needed. As more molecules are identified as markers, their use is likely to be greater in clinical practice. In summary, molecular diagnostics of brain tumour has proven to be an indispensable component of contemporary neuro-oncology with continued advances to enhance patient care and improve the diagnoses and prognosis of each patient's cancer (Horbinski et al., 2025).

6. Challenges and Future Perspectives

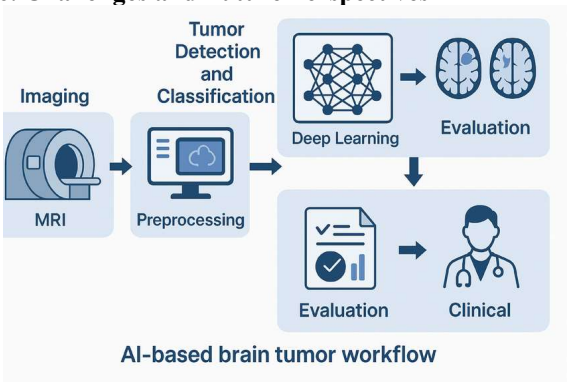

Figure 7: Artificial Intelligence Workflow for Brain Tumor Detection and Clinical Decision Support
(Source: https://www.researchgate.net/publication/398645135/figure/fig2)

6.1 Current Challenges

While molecular neuropathology has contributed to diagnosis of CNS tumors, there are still some obstacles in the way. The molecular testing is expensive and is not readily available in hospitals in low-resource settings. Testing methods and reporting procedures may vary from one lab to another, resulting in variation of the results between labs. To interpret the complex genetic data also, specially skilled experts and advanced laboratory facilities are needed. It is important to address these challenges to make molecular diagnosis more accurate, affordable and accessible to patients around the globe (Johnson et al., 2022). One of the obstacles is that there is limited standardization of molecular testing in various countries and health care systems. There are not as many trained specialists and advanced laboratory equipment in smaller hospitals. It is expected that escalating funding for molecular diagnostics laboratory infrastructure, professional training and collaboration in the international arena will help to further enhance the quality and uniformity of molecular diagnosis throughout the world.

6.2 Future Directions

The diagnosis and therapy of CNS tumors will benefit even more if further developments in the field of neuropathology continue in the future. **Liquid biopsy** is the potential of detecting tumors earlier and with less invasiveness by analysing blood samples. The incorporation of AI with digital pathology can enhance the speed and accuracy of diagnosis. Combination of multiple molecular data from **multi-omics** technologies will yield a more comprehensive understanding of tumor biology. The WHO classification also looks forward to discovering new biomarkers, which will further guide more personalized and accurate care for the patient. Further studies will also help advance the identification of novel molecular markers, which might be more predictive for treatment response. Comprehensive technologies and massive amounts of clinical data will facilitate rapid diagnoses, enhanced monitoring of disease, and more targeted treatment approaches, ultimately aiding in the long-term care and improvement of patients with CNS tumors.

7. Conclusion

It can be concluded that there have been significant advances in molecular neuropathology in the last few years which has revolutionized the concept of classification of CNS tumors using both histological and molecular tools. The classification according to WHO CNS5 and the important molecular markers have resulted in better diagnosis, prognosis and planning of treatment. As research progresses and new technologies develop, personalized medicine will continue to grow and yield more benefits to patients with CNS tumors. Future integration of researchers, clinicians, and health-care systems will be necessary if new studies are going to make their way into daily medical use. With the continuous evolution of molecular technologies, and of recent classification schemes, there is a prediction of further development of patient care and opportunities in the near future for advancing the field of precision neuropathology.

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