

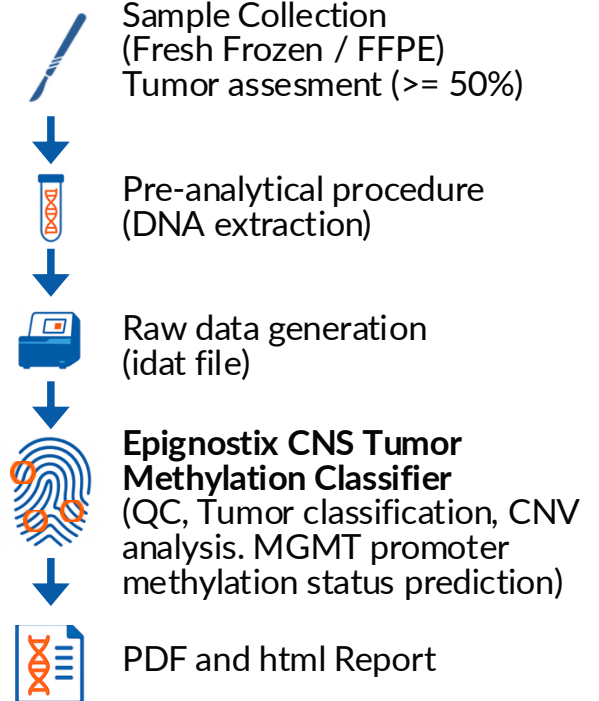


Epignostix CNS Tumor Methylation Classifier

Version 12.8

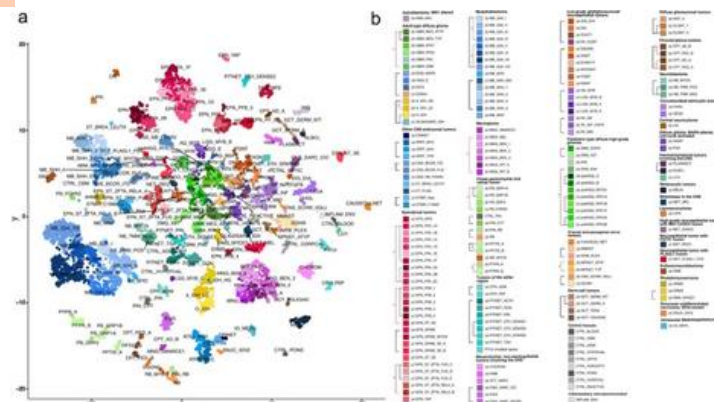
Released: April 2025

-  **184 subclasses**, 142 classes, 75 families
-  Reference cohort: **7,495 methylation profiles**
-  **95%** subclass-level accuracy
-  Four tier hierarchical output structure
-  Proposed evidence level annotation
-  **CE/IVD** expected in 2026
-  **150,000+** patient cases analyzed
-  **500+** institutions worldwide use the classifier



List of Super-Families Version 12.8

1. Adult-Type Diffuse Gliomas
2. Circumscribed Astrocytic Tumours
3. Central Neurocytoma
4. Cranial And Paraspinal Nerve Tumours
5. Control Tissues
6. Diffuse Glioma, Mapk Altered, Cell-Cycle Activated
7. Other CNS Embryonal Tumours
8. Ependymal Tumours
9. Germ Cell Tumours
10. Diffuse Glioneuronal Tumours
11. Haematolymphoid Tumours Involving The CNS
12. High-Grade Neuroepithelial Tumour With MN1:BEND2 Fusion
13. Inflammatory Microenvironment
14. Intraocular Medulloepithelioma
15. Low-Grade Glial/Glioneuronal/Neuroepithelial Tumours
16. Liponeurocytoma
17. Medulloblastoma
18. Melanocytic Tumours
19. Metastases To The CNS
20. Meningioma
21. Mesenchymal, Non-Meningothelial Tumours Involving The CNS
22. Neuroblastoma
23. High-Grade Neuroepithelial Tumour With MN1:CXXC5 Fusion
24. Neuroepithelial Tumour With PATZ1 Fusion
25. Neuroepithelial Tumour, PLAG1-Fused
26. Esthesioneuroblastoma
27. Paediatric-Type Diffuse High-Grade Gliomas
28. Pineal Parenchymal And Retinal Tumours
29. Choroid Plexus Tumours
30. Pineal Tumours
31. Rhabdomyosarcoma
32. Sinonasal Undifferentiated Carcinoma, IDH2-Mutant
33. Tumours Of The Sellar Region



Sill et al. (Cancer Cell, 2026)

-  On-premise version for routine use
-  Compatible with standard laptops
An installation guide is included.
-  RUO Platform freely accessible for academic research and scientific use
-  Register here:
<https://app.epignostix.com/>
-  Contact for more information
info@epignostix.com



Publications connected to the Epignostix CNS Tumor Methylation Classifier

Advancing CNS tumor diagnostics with expanded DNA methylation-based classification

Sill M. et al., *Cancer Cell* (2026)

DNA methylation-based classification is integral to contemporary neuro-oncological diagnostics, as highlighted by the current World Health Organization (WHO) classification of central nervous system (CNS) tumors. We introduce the Heidelberg CNS Tumor Methylation Classifier version 12.8 (v12.8), trained using 7,495 methylation profiles, thereby expanding recognized tumor types from 91 classes in the previously published v11 [1](#) to 184 subclasses in v12.8. This expansion was primarily driven by novel tumor types discovered in our large website-derived repository and through global collaborations, further elucidating the heterogeneity of CNS tumors. Utilizing a random forest-based methodology, the classifier was rigorously validated through five-fold nested cross-validation, achieving a 95% subclass-level accuracy and a Brier score of 0.028, indicative of well-calibrated probability estimates. The hierarchical output structure facilitates comprehensive interpretation, allowing clinicians to assess subclass and aggregate class-level probabilities for informed decision-making. Comparative analyses demonstrate that v12.8 surpasses previous versions as well as traditional WHO-based diagnostics across diverse tumor cohorts. These advancements underscore the enhanced precision and practical utility of the updated Heidelberg CNS Tumor Methylation Classifier, reinforcing the pivotal role of DNA methylation profiling in personalized neuro-oncological care.

Diffuse glioneuronal tumour with oligodendroglioma-like features and nuclear clusters (DGONC) – a molecularly defined glioneuronal CNS tumour class displaying recurrent monosomy 14

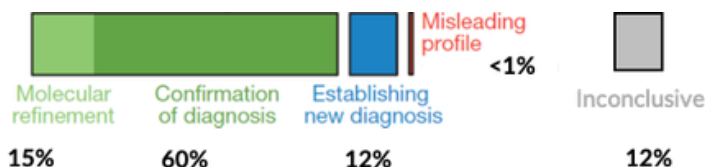
M.Y. Deng et al., *Neuropathology and Applied Neurobiology* 46, 422–430 (2020)

DNA methylation-based central nervous system (CNS) tumour classification has identified numerous molecularly distinct tumour types, and clinically relevant subgroups among known CNS tumour entities that were previously thought to represent homogeneous diseases. Our study aimed at characterizing a novel, molecularly defined variant of glioneuronal CNS tumour. Genome-wide DNA methylation data from over 25,000 CNS tumours were screened for clusters separated from established DNA methylation classes, revealing a novel group comprising 31 tumours, mainly found in paediatric patients. This DNA methylation-defined variant of low-grade CNS tumours with glioneuronal differentiation displays recurrent monosomy 14, nuclear clusters within a morphology that is otherwise reminiscent of oligodendroglioma and other established entities with clear cell histology, and a lack of genetic alterations commonly observed in other (paediatric) glioneuronal entities. Our study revealed the existence of a DNA methylation-defined class of low-grade glioneuronal tumours with recurrent monosomy 14, oligodendroglioma-like features and nuclear clusters.

DNA methylation-based classification of central nervous system tumours

Capper D. et al., *Nature* 555, 469–474 (2018)

Accurate pathological diagnosis is crucial for optimal management of cancer patients. For the ~100 known central nervous system (CNS) tumour entities, standardization of the diagnostic process has been shown to be particularly challenging - with substantial inter-observer variability in the histopathological diagnosis of many tumour types. We herein present the development of a comprehensive approach for DNA methylation-based CNS tumour classification across all entities and age groups and demonstrate its application in a routine diagnostic setting. We show that availability of this method may have substantial impact on diagnostic precision compared with standard methods, resulting in a change of diagnosis in up to 12% of prospective cases. For broader accessibility we have designed a free online classifier tool (www.moleculareuropathology.org) requiring no additional onsite data processing. Our results provide a blueprint for the generation of machine learning-based tumour classifiers across other cancer entities, with the potential to fundamentally transform tumour pathology.



Multimic neuropathology improves diagnostic accuracy in pediatric neuro-oncology

Sturm D. et al., *Nature Medicine* 29, 917–926 (2023)

The large diversity of central nervous system (CNS) tumor types in children and adolescents results in disparate patient outcomes and renders accurate diagnosis challenging. In this study, we prospectively integrated DNA methylation profiling and targeted gene panel sequencing with blinded neuropathological reference diagnostics for a population-based cohort of more than 1,200 newly diagnosed pediatric patients with CNS tumors, to assess their utility in routine neuropathology. We show that the multi-omic integration increased diagnostic accuracy in 85% of cases, including 36% with refined diagnosis and 13% with major diagnostic changes. The integration of molecular data also enabled the identification of diagnostically or therapeutically relevant alterations in 31% of cases. Our study demonstrates the feasibility and utility of integrating molecular profiling into routine diagnostics for pediatric CNS tumors, leading to improved diagnostic precision and potential therapeutic implications.

