

Patient Name: Jane Doe
Specimen ID: ADM52A5864
Order ID: LP1000571

Test: JAX OncoMethyl™ Array – CNS Tumors
Report Date: 11/19/2024

Demographics

PATIENT	SPECIMEN	PHYSICIAN
Name: Jane Doe	Specimen ID: ADM52A5864	Name: Bart Bass
Patient ID: JL1000485	Source Specimen ID: XX-24-9999	Affiliation: JAX-Lab-Internal-Quality
Source Patient ID: 1112223	1° Tumor Site: Brain	
D.O.B: 01/01/1951	Specimen Site: Brain	
Sex: Female	Neoplastic Content: 75%	
Submitted Diagnosis: High grade glioma	Collection Date: 11/13/2024	
	Received Date: 11/13/2024	

Methylation Profiling Results (MNP v12epicv2_0.1.136)

Classification Level	Methylation Classification	Calibrated Score*
Superfamily	Adult-type diffuse gliomas	0.9999
Family	Glioblastoma, IDH-wildtype	0.9999
Class	glioblastoma, IDH-wildtype, RTK2 type	0.9999
Subclass	Glioblastoma, IDH-wildtype, RTK2 subtype	0.9999

*Calibrated scores represent an estimated likelihood measure of methylation class assignment. A score of 0.84 and above is considered a high measure of correct methylation class assignment. As per the WHO 2021 classification of central nervous system tumors, pathologists should be wary about endorsing suggested diagnoses with scores below 0.84 and should discard recommendations if scores are below 0.50¹. The JAX OncoMethyl™ Array has been validated for samples with calibrated scores ≥ 0.50 only.

NOTE: The methylation profiling and classifier are intended to provide supplementary information for diagnosis. The final diagnosis should be performed by qualified pathologists.

Additional Information

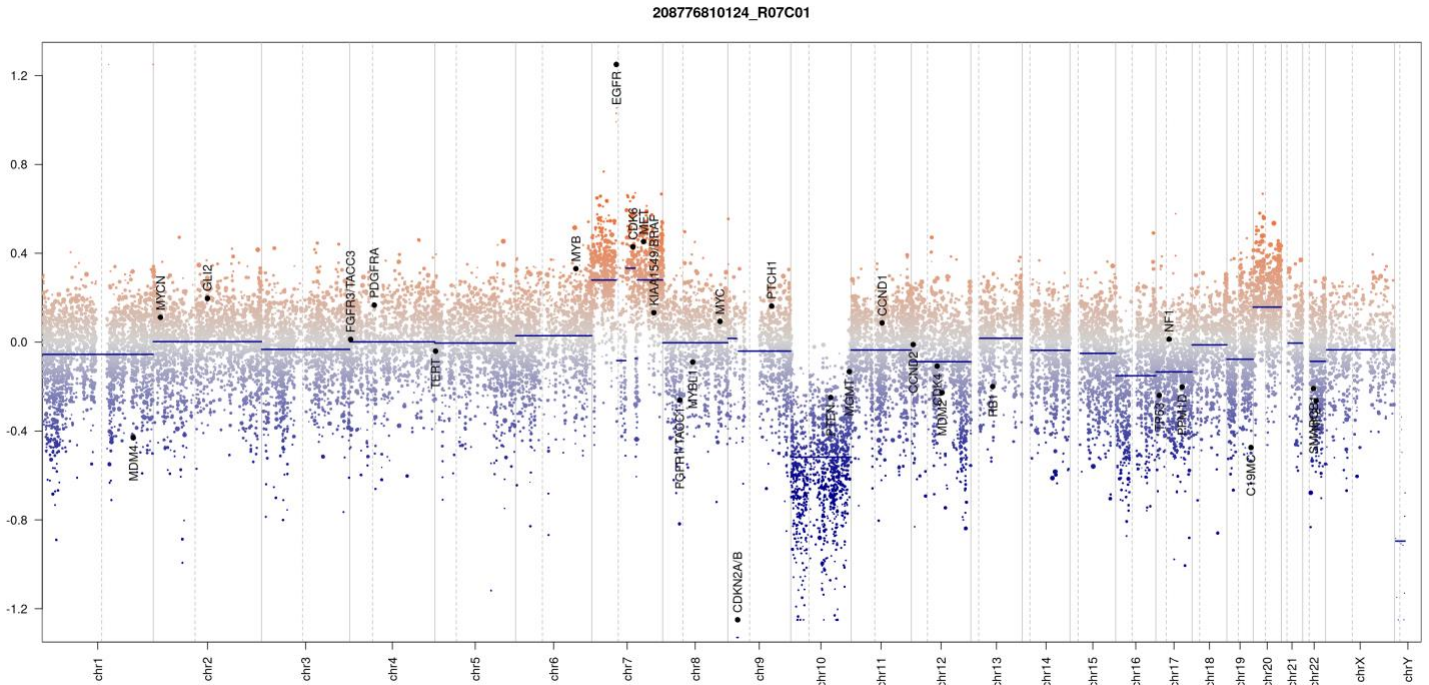
Glioblastoma, IDH-wildtype, RTK2 subtype:

The "mc Glioblastoma, IDH-wildtype, RTK2 subtype" is comprised of diffuse, astrocytic gliomas that are IDH-wildtype and H3-wildtype and have one or more of the following histological or genetic features: microvascular proliferation, necrosis, TERT promoter mutation, EGFR gene amplification, +7/-10 chromosome copy-number changes (CNS WHO grade 4). They also very commonly (~90%) harbor TP53 mutations and CDKN2A/B deletions (~70%). They can manifest in patients of any age but preferentially affect older adults, with peak incidence in patients aged 55–85 years. The RTK2 subtype harbours a high frequency of EGFR amplification (~60%). Expression profiles often resemble the 'Proneural' subgroup according to the TCGA classification. Expression profiles often resemble the 'Classical' subgroup according to the TCGA classification.

MGMT Promoter Methylation Status:

Methylated

Copy Number Variation Profile** (Research use only; not clinically validated)



Depiction of chromosomes 1-22 (and X/Y if automatic prediction was successful). Copy number gains/amplifications are shown as positive deviations (orange), while copy number losses are shown as negative deviations (blue) from the baseline. 29 relevant gene regions are highlighted for reference².

****Based on the whole genome methylation array. Resolution of this array is insufficient to confidently call CNV events. CNV results should be confirmed using an alternative method.**

Test Methods & Limitations

As necessary (for FFPE blocks or unstained slides), specimens are sectioned and stained using Fisher Chemical Eosin Y and Richard-Allan Scientific™ Hematoxylin Stain (Modified Mayer). Slides are digitally scanned on the Leica Aperio CS2 Scanner for remote pathologist review of neoplastic content, tissue type, tumor area, and specimen quality (Remote Testing Site: LBH07).

The JAX OncoMethyl™ Array utilizes a machine learning algorithm for the classification of central nervous system (CNS) tumors based on genomic methylation profiling data. The JAX OncoMethyl™ Array uses genomic DNA extracted from FFPE tissues (≥70% neoplastic content) that is followed by bisulfite conversion (Zymo Research). Converted DNA undergoes whole genome amplification and is processed utilizing the Infinium MethylationEPIC Array v2 (Illumina). Raw IDAT files are processed through the CNS methylation classifier developed by the Molecular Neuropathology group at the German Cancer Research Center (DKFZ)³. Methylation Class Family and Methylation Class calibrated scores are provided by the classifier (v12.8). During validation, 98% of samples with Methylation Class calibrated scores ≥0.84 were considered “classifiable” and resulted in either confirmation, refinement, or reassignment of diagnosis.

MGMT promoter methylation status is assessed using a logistic regression model (MGMT-STP27) comprising probes cg12434587 and cg12981137⁴. Results are reported relative to the established cutoff of 0.3582 as: “Methylated” if the estimated methylation and confidence intervals are above the established cutoff; “Unmethylated” if estimated methylation and confidence intervals are below the established cutoff; or “Indeterminate” if the lower confidence interval is below, and the upper confidence interval is above the established cutoff.

Review of digital data, results, and/or clinical report was performed at the following remote testing sites: MKH11.

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References

- ¹Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol.* 2021 Aug 2;23(8):1231-1251. doi: 10.1093/neuonc/noab106. PMID: 34185076; PMCID: PMC8328013.
- ²Daenekas B, Pérez E, et al. Conumee 2.0: enhanced copy-number variation analysis from DNA methylation arrays for humans and mice. R package version 2.0, <https://github.com/hovestadtlab/conumee2>.
- ³Capper D, Jones DTW, Sill M, et al. DNA methylation-based classification of central nervous system tumours. *Nature.* 2018 Mar 22;555(7697):469-474. doi: 10.1038/nature26000. PMID: 29539639; PMCID: PMC6093218.
- ⁴Bady P, Sciuscio D, Diserens AC, et al. MGMT methylation analysis of glioblastoma on the Infinium methylation BeadChip identifies two distinct CpG regions associated with gene silencing and outcome, yielding a prediction model for comparisons across datasets, tumor grades, and CIMP-status. *Acta Neuropathol.* 2012 Oct;124(4):547-60. doi: 10.1007/s00401-012-1016-2. Erratum in: *Acta Neuropathol.* 2013 Jul;126(1):159. PMID: 22810491; PMCID: PMC3444709.

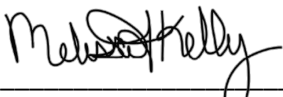
Disclaimer

Decisions on patient care must be based on the independent medical judgment of the treating physician, taking into consideration all relevant information about the patient's condition, including patient medical and family history, physical examinations, information from other diagnostic tests, and patient preferences. A treating physician's decisions should not be based on a single test, such as this test, or the information contained in this report alone. Results of this test must always be interpreted in the context of all relevant clinical and pathological data and should not be used alone for diagnosis or patient care decisions. Genetic counseling is recommended to discuss the implications of these test results.

The JAX OncoMethyl™ Array uses a machine learning algorithm to classify central nervous system cancers based on genomic methylation profiling. As per the WHO 2021 classification of central nervous system tumors, careful attention must be paid to the common calibrated score threshold and pathologists should be wary about endorsing suggested diagnoses with scores below 0.84, and scores below 0.50 are reported as "inconclusive" or "no match". As with other diagnostic tests, the pathologist must take into account histological features (e.g., tumor cell amount and purity) when interpreting results¹. Tumor tissue is not homogenous, and its characteristics may differ from sample to sample for the same tumor. Sample neoplastic content levels near the required minimum (70%) may have decreased classification scores.

The Jackson Laboratory expressly disclaims and makes no representation or warranty relating to the published evidence and scientific literature identified in this report, or any of the conclusions and information set forth in this report that is derived from a review thereof, including information and conclusions relating to therapeutic agents that are included or omitted from this report.

This test was developed, and its performance characteristics determined by The Jackson Laboratory. It has not been cleared or approved by the U.S. Food and Drug Administration (FDA). This laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA 88) as qualified to perform high complexity clinical testing. The Jackson Laboratory makes no promises or guarantees that a healthcare provider, insurer, or other third-party payor, whether private or governmental, will reimburse a patient for the cost of this test.



Melissa Kelly, PhD, HCLD/CC(ABB), Clinical Laboratory Director

2024-11-19

Date