Real-world data enables large-scale assessment of WHO CNS5 glioma classification

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Joshuah Kapilivsky[1], Kimmo J Hatanpaa[2], Kabir Manghnani[1], Timothy Taxter[1], Martin C Stumpe[1], Justin Guinney[1], Kyle Beauchamp[1,*], Robin A Buerki[3], and Alessandra Breschi[1,*]

[1]Tempus Labs, Inc., Chicago, IL // [2]Division of Pathology, University of Texas Southwestern Medical Center, Dallas, TX // [3]Division of Neuro-oncology, Northwestern Medicine, Chicago, IL // ***Correspondence:** publications@tempus.com

INTRODUCTION

In 2021, the WHO revised its classification of central nervous system tumors (WHO CNS5) around IDH status and inclusion of key somatic alterations, in addition to histopathological traits. While providing a more specific classification system for patients, the guidelines introduce new logistical challenges for pathologists by relying on multi-modal data. In this study, we use a combined clinical / molecular real world dataset to reclassify a cohort of adult-type diffuse gliomas and evaluate prognostic impact using real-world overall survival (rwOS).

METHODS

We retrospectively analyzed a de-identified dataset of 2,703 samples profiled via the Tempus xT assay (DNA-seq of 595-648 genes at 500x coverage, whole-exome capture RNA-seq). Original diagnoses were identified from sample pathology reports. Samples were excluded if the original diagnosis or molecular findings indicated a pediatric-type glioma or did not specify beyond diffuse glioma. Molecular features were derived from NGS testing; necrosis and microvascular proliferation were inferred from gene expression profiles using machine learning. rwOS was defined as time from original diagnosis until death. To account for left truncation, samples were only considered at risk of death after study entry (*e.g.*, date of sequencing if sequenced as part of clinical care). RNA-seq data was visualized using principal components analysis followed by uniform manifold approximation & projection.

WHO CNS5 Glioma classification definitions

Astrocytoma, *IDH*-mut, Grade 2/3
Diagnostic: ***IDH*-mutant**
Supporting: *ATRX* Inactivation
Absent: 1p/19q Codeletion, MVP, Necrosis, *CDKN2A/B* Homozygous Deletion

Astrocytoma, *IDH*-mut, Grade 4
Diagnostic: ***IDH*-mutant;** MVP, Necrosis, OR *CDKN2A/B* Homozygous Deletion
Supporting: *ATRX* Inactivation
Absent: 1p/19q Codeletion

Oligodendroglioma, *IDH*-mut, 1p/19q, Grade 2/3
Diagnostic: ***IDH*-mutant AND 1p/19q Codeleted**
Supporting: *TERT* Promoter Mutation

Glioblastoma, *IDH*-wt, Grade 4
Diagnostic: ***IDH*-wildtype AND *H3*-wildtype**
MVP, Necrosis, *TERT* promoter mutation, *EGFR* amplification, OR chromosome 7 gain/10 loss

Table 1. While previous guidelines use histologic features as the initial diagnostic criterion, WHO CNS5 relies on both molecular and histologic features to categorize adult-type diffuse gliomas.

SUMMARY

Comprehensive **molecular profiling** enables the application of **WHO CNS5 guidelines** and alters diagnoses in a retrospective, real-world dataset of adult-type diffuse gliomas.

WHO CNS5-based diagnoses **more accurately stratify** patients according to risk and underlying molecular phenotypes.

RESULTS

WHO CNS5 classification requires multi-modal data

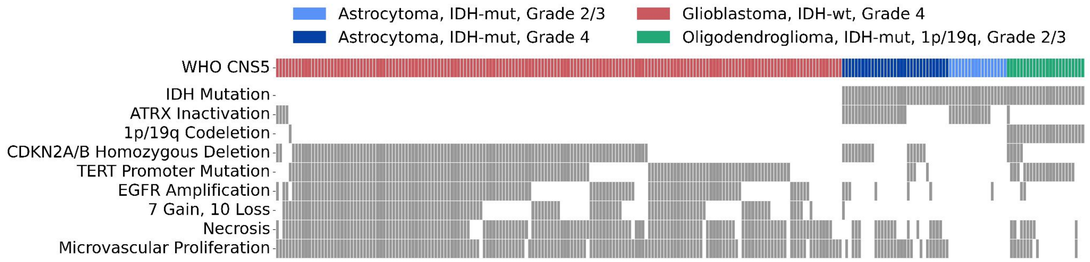
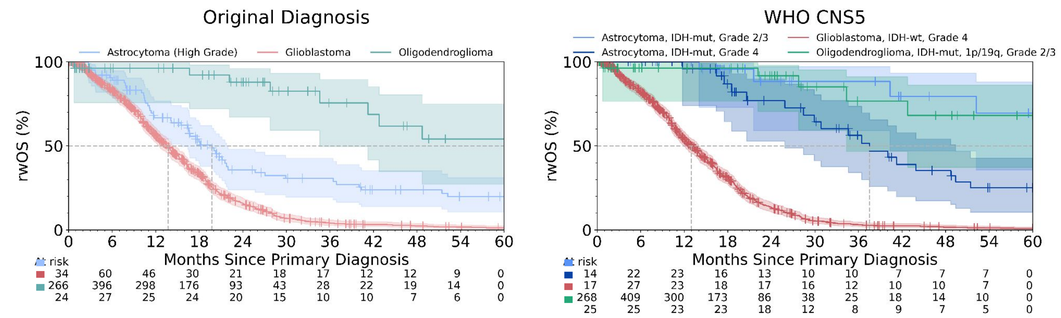


Figure 1. Features used to reclassify samples under WHO CNS5, including grade stratification of Astrocytoma, *IDH*-Mut (shown above for 250 randomly selected patients). Each column represents a single patient; colored bars show WHO CNS5 reclassification and gray bars indicate the presence of the feature for that particular patient. Among patients with *IDH* mutations, 16% had an *IDH* mutation other than *IDH1* p.R132H.

rwOS data shows improved prognostic stratification under WHO CNS5



Original Diagnosis	N	Events	HR	95% CI	p-value
Overall Model					*3e-23*
Astrocytoma (High Grade)	115	49	0.47	0.35, 0.63	4e-07
Glioblastoma	807	513	-	-	-
Oligodendroglioma	58	8	0.11	0.06, 0.23	9e-10

WHO CNS5	N	Events	HR	95% CI	p-value
Overall Model					*7e-46*
Astrocytoma, *IDH*-mut, 2/3	41	4	0.07	0.03, 0.18	8e-08
Astrocytoma, *IDH*-mut, 4	68	18	0.18	0.11, 0.28	5e-13
Glioblastoma, *IDH*-wt, 4	821	543	-	-	-
Oligodendroglioma, *IDH*-mut, 1p/19q, 2/3	50	5	0.08	0.03, 0.20	3e-08

Figure 3. We compared the ability of original diagnosis and WHO CNS5 reclassifications to stratify real world overall survival (rwOS, n=980). While both label sets are individually prognostic, adding WHO CNS5 to original diagnoses leads to a statistically significant improvement in prognostic stratification (likelihood ratio test; P < 2e-24). Notably, the median survival for WHO CNS5 reclassification of "Astrocytoma, *IDH*-mut, Grade 4" is 38 months, nearly twice the 20 months for an original diagnosis of astrocytoma. This is largely attributable to reclassification of the higher risk astrocytoma patients into "Glioblastoma, *IDH*-wt, Grade 4".

Samples originally diagnosed as astrocytoma are heterogeneously classified under WHO CNS5

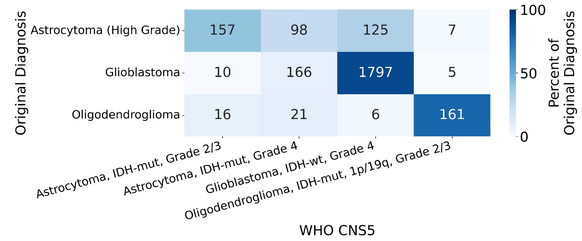


Figure 2. WHO CNS5 reclassification of patients (n=2,569). Samples with an original diagnosis of astrocytoma, for instance, received the following WHO CNS5 diagnoses: 41% Astrocytoma, *IDH*-mut, Grade 2/3; 25% Astrocytoma, *IDH*-mut, Grade 4; and 32% Glioblastoma, *IDH*-wt, Grade 4.

Whole-exome RNA-seq data more closely aligns with WHO CNS5

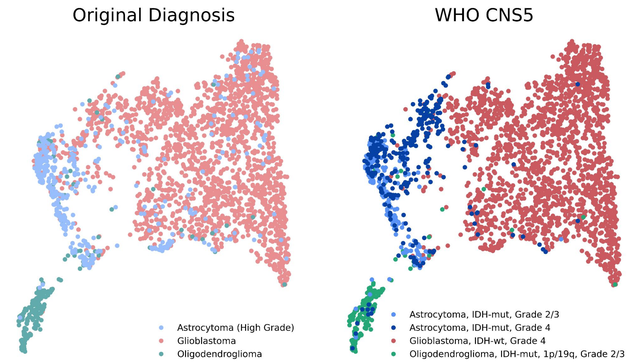


Figure 4. We reduced whole-exome RNA-seq data to two dimensions and visualized it by original diagnosis and WHO CNS5 (n=2,569). Both visualizations show clear clustering by diagnosis, with some overlap. We found that WHO CNS5 types (i.e., not including grade) form clusters that are more cohesive and separate than original diagnoses (silhouette scores 0.45 and 0.28; higher is better).

References: WHO Classification of Tumours Editorial Board. Central nervous system tumours. WHO classification of tumours series, 5th ed.; vol. 6.