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ΕΚΘΕΣΗ ΑΠΟΤΕΛΕΣΜΑΤΩΝ ΕΞΕΤΑΣΗΣ

Στοιχεία Εξεταζόμενου		Στοιχεία Παραπομπής	
Εξεταζόμενος	-	**Νοσοκομείο/Κλινική**	-
Ημερ. Γέννησης	-	**Αρ. Έκθεσης ΠΑ**	-
ΑΜΚΑ	-	**Κλινική Διάγνωση**	ΟΛΙΓΟΔΕΝΔΡΟΓΛΟΙΩΜΑ
Παραπέμπων	-		

Στοιχεία Δείγματος			
Τύπος Δείγματος #1	ΙΣΤΟΣ ΕΓΚΛΕΙΣΜΕΝΟΣ ΣΕ ΜΠΛΟΚ ΠΑΡΑΦΙΝΗΣ	**Ημερ. Παρ. Δειγμ.**	-
Κωδικός Δείγματος #1	-	**Ημερ. Αποτελ.**	-
Εκτιμώμενο TCC	60%	**Ποιοτικός Έλεγχος Δείγμ.**	Αποδεκτό
Macrodissection	Ναι	**Barcode**	26xxxxxxGR

Αποτελέσμα Μοριακής Ανάλυσης

Βιοδείκτης	Αποτέλεσμα	Σχόλιο
IDH1	Εξώνιο 4 c.395G>A, p.R132H (VAF 41.1%)	Πίνακας 1
CIC	Εξώνιο 20 c.4533_4535delCCGinsTCT, p.R1512L (VAF 75.7%)	Πίνακας 1
FUBP1	Εξώνιο 16 c.1519_1528del, p.P507Gfs*155 (VAF 73.2%)	Πίνακας 1
TERT	c.-146C>T, (C250T) (VAF 42.4%)	Πίνακας 1
Μικροδορυφορική Αστάθεια (MSI)	Χωρίς μικροδορυφορική αστάθεια (MSS)	
Υποκινητής MGMT	Μεθυλιωμένος	
1p19q	Ανιχνεύθηκε συν-έλλειψη των χρωμοσωμικών περιοχών 1p19q	Πίνακας 1

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Γιώργος Νασιούλας, PhD Μοριακός Βιολόγος, Επιστημονικός Διευθυντής, ΑΜΚΑ:26025301255
Κωδικός Εγγράφου: Δ21_GlioGene

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Patient Information		Referral Information	
Name	-	**Institution/Clinic**	-
Date of Birth	-	**Pathology Report No.**	-
ID/Medical ID	-	**Clinical Diagnosis**	GLIOBLASTOMA
Req. Physician	-		

Sample Details			
Type of sample #1	PARAFFIN EMBEDDED TISSUE-BLOCK	**Date Received**	-
Code of sample #1	-	**Date of Report**	-
Estimated TCC	70%	**Sample QC**	Pass
Macrodissection	Yes	**Barcode**	26xxxxxxGR

Molecular Analysis Results

Biomarker	Result	Comment
IDH1	Exon 4 c.395G>A, p.R132H (VAF 41.1%)	Table 1
CIC	Exon 20 c.4533_4535delCCGinsTCT, p.R1512L (VAF 75.7%)	Table 1
FUBP1	Exon 16 c.1519_1528del, p.P507Gfs*155 (VAF 73.2%)	Table 1
TERT	c.-146C>T, (C250T) (VAF 42.4%)	Table 1
Microsatellite Instability (MSI)	Stable (MSS)	
MGMT promoter	Methylated	
1p19q	1p19q co-deletion detected	Table 1

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George Nasioulas, PhD Molecular Biologist, Scientific Director, Medical ID:26025301255

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Interpretation

Genetic Variation:	*IDH1*: c.395G>A (p.R132H)	VAF*: 41.1%	OncoKB

Gene information

The IDH1 (isocitrate dehydrogenase 1) protein is an enzyme that catalyzes the oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG), a crucial step in the tricarboxylic acid (TCA) cycle. IDH1 utilizes NADP(+) as an electron acceptor and it is predominantly expressed in the cytosol and peroxisomes, playing a role in the cytoplasmic production of NADPH. Cancer-associated mutations in the catalytic site of IDH1 confer a gain-of-function of neomorphic enzymatic activity, allowing the mutant enzyme to convert α-KG to the "oncometabolite" D-2-hydroxyglutarate (2-HG) (PMID: 20171147). 2-HG promotes tumor development by inhibiting a variety of enzymes that require α-KG as a substrate, including enzymes involved in DNA demethylation, histone demethylation, adaptation to hypoxia and collagen maturation. IDH1 mutations have been identified in glioma, cholangiocarcinoma and acute myeloid leukemia (AML) among others (PMID: 19657110, 23630074) and may contribute to the progression of myeloproliferative neoplasms to bone marrow failure or AML (PMID: 29355841).

Variant Information

The IDH1 R132H mutation is located in the catalytic site of the IDH1 protein. This mutation has been found in acute myeloid leukemia and gliomas, among others (PMID: 19935646, 29860938). In vitro and in vivo studies have demonstrated that this mutation changes IDH1 enzymatic activity, allowing for the conversion of α-ketoglutarate (α-KG) to the "oncometabolite" D-2-hydroxyglutarate (2-HG), and leads to oncogenic activity, as evidenced by aberrant changes in DNA methylation, cytokine independence, dedifferentiation and in vivo increases in early hematopoietic progenitors compared to wildtype IDH1 (PMID: 19935646, 22763442, 23393090). IDH1 mutations at the R132 residue, including the R132H mutation are central to WHO CNS5 classification of diffuse gliomas and this classification now has direct therapeutic weight, since the IDH1/2-targeted inhibitor vorasidenib is FDA-approved for the treatment of patients twelve years and older with astrocytoma or oligodendroglioma with a susceptible IDH1 mutation.

Genetic Variation:	*CIC*: c.4533_4535delCCGinsTCT (p.R1512L)	VAF*: 75.7%	OncoKB

Gene information

CIC (also Capicua) is a transcriptional repressor that is a member of the high mobility (HMG)-box protein family (PMID: 32073140). CIC is expressed in a variety of tissues and is a critical regulator of patterning, differentiation, and signaling (PMID: 10652276, 32073140). Chromatin modifiers, such as the Sin/HDAC3 histone deacetylase complex, are recruited to sites bound by CIC to inhibit gene expression of target genes (PMID: 29844126). CIC exists in diverse protein complexes including with ATXN1, which directly binds CIC and modulates its transcriptional repressor activity (PMID: 17190598). The CIC-ATXN1 complex regulates the expression of several transcription factors, including members of the ETS protein family (PMID: 27869830). Loss of CIC expression results in the derepression of ETS transcriptional regulators, such as ETV4, which can activate extracellular remodeling programs and metastasis (PMID: 27869830, 22014525). In addition, CIC is a negative regulator of receptor tyrosine kinase (RTK) and MAPK signaling pathways and acts as a transcriptional repressor in the absence of RTK signaling (PMID: 11714680, 11861482, 29844126, 28178529). CIC is recurrently mutated in oligodendrogliomas, including in 1p/19q-deleted cancers (PMID: 21817013, 22869205, 22588899). Somatic mutations and deletions have also been found in various other cancer types, including in lung and gastric cancers (PMID: 25079317, 27869830). Chromosomal translocations that produce chimeric CIC proteins fused to several partner proteins, including

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DUX4 or FOXO4, occur in aggressive round cell sarcomas and result in aberrant CIC-mediated transcriptional activation (PMID: 19837261, 25007147, 21813156).

Variant Information

There is no available functional data about the CIC R1512L mutation (However, it has been identified as a statistically significant hotspot and is likely to be pathogenic.

Genetic Variation:	*FUBP1*: c.1519_1528del (p.P507Gfs*155)	VAF*: 73.2%	OncoKB

Gene information

The protein FUBP1, binds single-stranded DNA, including regulatory DNA elements upstream of genes. Among the motifs it binds is the far upstream element (FUSE), which is located upstream of the MYC oncogene (PMID: 22926519). Regulation of MYC by FUBP1 is complex; while overexpression of FUBP1 can activate transcription of the MYC gene, it has also been reported that inactivating mutations of FUBP1 activate MYC expression (PMID: 20420426). FUBP1 is also known to bind RNA (PMID: 23818605), such as in order to regulate the splicing of MDM2, an important negative regulator of the tumor suppressor TP53 (PMID: 24798327). FUBP1 was reported to be mutated at relatively low frequency (<8%) across a variety of cancers (cBioPortal, Nov 3, 2015). It is most frequently mutated in gliomas, which also show frequent deletion of 1p, where the FUBP1 gene is located (PMID: 22869205, 21817013).

Variant Information

FUBP1 truncation mutations occur throughout the gene and are associated with decreased FUBP1 protein expression (PMID: 24117486). Loss of FUBP1 on chromosome 1p is associated with IDH1 and CIC mutations on chromosome 19q in gliomas (PMID: 24117486, 22072542, 21817013). In vitro studies with HEK293 cells expressing central DNA-binding domain truncated FUBP1 demonstrate that FUBP1 truncation mutations are inactivating as measured by reduced transcriptional activity compared to full-length FUBP1 (PMID: 30500954). The FUBP1 P507Gfs*155 is a truncating mutation in a tumor suppressor gene, and therefore is likely pathogenic.

Genetic Variation:	*TERT*: c.-146C>T (C250T)	VAF*: 42.4%	OncoKB

Gene information

The TERT gene encodes the catalytic subunit of telomerase, an enzyme that maintains telomere length and genomic integrity. TERT expression is low or absent in somatic cells; however, telomerase activity is upregulated in a vast majority of tumors and likely contributes to cancer cell immortality (PMID: 24657534, 9282118). Sequencing of the TERT promoter identified activating mutations in a number of cancer types including melanoma, hepatocellular carcinoma, urothelial carcinoma, medulloblastoma and glioma (PMID: 23348506, 23530248). Tumors with highly recurrent TERT promoter mutations tend to originate from tissues with lower rates of self-renewal (PMID: 23530248). TERT promoter mutations, C228T and C250T, account for the majority of the somatic TERT promoter alterations and occur 124 and 146 base pairs upstream of the ATG start codon of TERT, respectively. Both promoter mutations create binding motifs for erythroblast transformation-specific (ETS)/ T-cell factor (TCF) transcription factors and enhance telomerase activity (PMID: 23348503, 23348506, 26194807). In addition to promoter mutations, TERT, located on chromosome 5p, is amplified across many cancer types (PMID: 20164920).

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Genetic Variation:	***MGMT* promoter: Methylated**	**VAF*: N/A**

Gene information

O6-methylguanine-DNA methyltransferase (MGMT) is a DNA repair gene located on chromosome 10q26 that encodes a repair enzyme responsible for removing alkyl adducts from the O6 position of guanine. This enzyme plays a critical role in maintaining genomic integrity by reversing DNA damage induced by alkylating agents such as temozolomide (TMZ). The MGMT promoter methylation status is a well-established epigenetic biomarker in CNS tumors, particularly in glioblastoma (GBM) and lower-grade gliomas. Methylation of CpG islands within the MGMT promoter leads to transcriptional silencing of the gene, thereby reducing the tumor cells' capacity to repair alkylating agent-induced DNA damage — sensitizing the tumor to chemotherapy.

MGMT promoter methylation is associated with a favorable prognostic and predictive outcome in patients with high-grade gliomas (PMID: 28266716, 36012105). This result supports the likelihood of therapeutic benefit from alkylating agent-based regimens.

Genetic Variation:	**1p19q: Co-deleted**	**VAF*: N/A**

Gene information

1p/19q codeletion refers to the combined whole-arm deletion of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q). This chromosomal alteration arises from an unbalanced translocation — t(1;19)(q10;p10) — resulting in the simultaneous loss of genetic material from both arms. It is one of the most important molecular hallmarks in neuro-oncology and is considered a defining genetic event in the classification of diffuse gliomas (PMID: 34185076).

1p/19q codeletion carries significant prognostic and predictive value. Patients harboring this alteration have demonstrated markedly improved overall survival and progression-free survival compared to non-codeleted gliomas of equivalent histological grade. Furthermore, co-deleted tumors exhibit enhanced sensitivity to alkylating chemotherapy (PMID: 28340142). The detection of this codeletion supports a diagnosis within the oligodendroglial spectrum and is associated with a more favorable long-term clinical course (PMID: 34185076).

*VAF: Variant Allele Frequency

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Methodology

DNA based NGS analysis

DNA was extracted from the sample under investigation using the MagMax Total Nucleic Acid Isolation Kit (ThermoFisher). A capture based targeted next generation sequencing (NGS) analysis was performed, using the Oncology Multi-Gene Variant Assay (GenePlus) which is a qualitative in vitro diagnostic test. The analysis of 29 genes includes the entire exon regions and CNVs of 9 genes, partial exon regions of 20 genes and introns/promoters/fusion breakpoint regions of 10 genes. The test also reports on Microsatellite Instability (MSI) status. Sequencing was carried out on an MGI sequencing platform (DNBSEQ-T7).

Sequencing data are analyzed through bioinformatics pipeline for variant calling and interpretation using the Gene+Box data analysis and management system.

Sensitivity: Positive reference standards are tested with the assay, all corresponding mutation sites can be accurately detected, and the positive percent agreement (PPA) for all variants (SNVs, Indels, fusions and CNVs) assessed was 100%.

Specificity: Negative reference standards are tested with the assay, and the negative percent agreement (NPA) of SNVs, Indels, fusions and CNVs was 100%.

Limit of Detection (LoD): The limit of detection (LoD) of this assay is listed in the table below. The LoD is based on as low as 50 ng of gDNA input for library preparation. The assay can also be used to test microsatellite instability (MSI) with a tumor cell content as low as 10%.

Tumor Type	Limit of Detection
Single nucleotide variations (SNV)	Hotspot: VAF ≥2%; Non-hotspot: VAF ≥5%
Insertions/deletions (Indel)	Hotspot: VAF ≥2%; Non-hotspot: VAF ≥5%
Fusion (or rearrangement)	VAF ≥2%

***MGMT* promoter gene methylation**

The CE-IVD geneMAP™ Methylation Analysis methylation-specific Realtime PCR (MSP) kit was used for the detection of MGMT promoter methylation in combination with the QuantStudio 3 Real Time PCR System (ThermoFisher) platform. Interpretation of results was conducted according to the manufactures instructions.

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Quality Control Results

Quality Control Index		Result	Criteria
Sequencing Quality Assessment	Average effective sequencing depth[1]	**760**	≥ 500
	Fraction of target covered with ≥ 50x[2]	100%	≥99%
	Fraction of base quality ≥ Q30[3]	99%	≥80%
Tumor cell content[4]		60%	60%
Overall Assessment[5]		PASS	

Note:

1. Average effective sequencing depth: Average sequencing depth on target without duplicated reads.
2. Fraction of target covered with ≥ 50x: The proportion of bases that sequencing depth reach or above 50x on target, this index reflecting the coverage uniformity of sequencing.
3. Fraction of base quality ≥ Q30: The proportion of base quality in sequencing data that reach or above Q30, that is the probability of base recognition accuracy rate exceeds 99.9%.
4. An overall tumor cell content percentage of ≥ 20% is recommended for the efficient detection of somatic alterations in the sample analyzed.
5. Overall Assessment: The quality control overall assessment results are divided into two levels: "PASS" and "RISK". When the overall quality assessment result is "RISK", 94-96% of coverage was achieved in the genes analysed, hence there is a small range where clinical actionable variations could be undetected.

Disclaimer

1. This test is mainly used to assist clinical decision-making, and the result does not represent clinical decision.
2. The test should be interpreted by combining the actual patient context.
3. As evidence on variants and drugs evolves, previous classifications may later be modified. The interpretation of a variant is based on current available evidence.
4. Sequence variants were reported using Human Genome Variation Society (HGVS) nomenclature. Classification and interpretation of variants follow guidelines of American College of Medical Genetics and Genomics (ACMG), Association of Molecular Pathology (AMP), American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP).
5. Database and references used: Reference genome (GRCh37), annotation using A Locus Reference Genomic (LRG), database referencing 1000G (phaseIII-ucsc), EXAC (0.3.1), dbSNP (147), PolyPhen2/SIFT (ensdb v73), PhyloP (2013-12-06), Clinvar (2018-8) and Cosmic(V80).

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Limitations

1. The test is limited to test genomic variations on DNA level and does not involve RNA level or protein level.
2. Scientific data show that not all patients carry genomic variations that are associated with targeted drug, therefore not all subjects can be matched with targeted therapies or clear resistance mechanism.
3. Genetic variation beyond the detection range of this test or some non-gene mutation related factors such as drug interactions may affect the clinical effects of drugs.
4. Fraction of base quality ≥ Q30: The proportion of base quality in sequencing data that reaches or exceeds Q30, indicating that the probability of base recognition accuracy rate exceeds 99.9%.
5. Every molecular test has an internal 0.5-1% chance of failure. This is due to rare molecular events and factors related to the preparation and analysis of the samples.
6. Improper sample collection, transportation and storage may lead to compromised or invalid results.

Genes Analyzed

29 gene alterations									
*ATRX**	*BRAF**	*CDKN2A**	*CDKN2B**	*CIC**	*CTNNB1**	*EGFR**	*ERBB2**	*FUBP1**	*H3F3A*
HIST1H3B	*HIST1H3C*	*IDH1*	*IDH2*	*MET*	*MYC*	*MYCN*	*MYD88*	*NF1*	*NF2*
PTCH1	*SMARCA4*	*SMARCB1*	*SMO*	*SUFU*	*TERT*	*TP53*	*TSC1*	*TSC2*	
10 fusions									
ALK	*BRAF*	*FGFR1*	*FGFR2*	*FGFR3*	*NTRK1*	*NTRK2*	*NTRK3*	*RET*	*ROS1*
***MGMT* methylation**									
1p19q co-deletion**									

**CNV (amplification/deletion) analysis is included for these genes*
***1p19q is tested only when an IDH1/IDH2 mutation is detected.*

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Table 1.

Diagnosis-Related gene alterations, included in the panel based on 2021 WHO classification of CNS tumors	
Tumor Type	**Genes Altered**
Astrocytoma, IDH-mutant	*IDH1*, *IDH2*, *ATRX*, *TP53*, *CDKN2A/B*
Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted	*IDH1*, *IDH2*, 1p/19q, *TERT* promoter, *CIC*, *FUBP1*
Glioblastoma, IDH-wildtype	IDH-wildtype, *TERT* promoter, *EGFR*
Polymorphous low-grade neuroepithelial tumor of the young	*BRAF*, FGFR family
Diffuse low-grade glioma, MAPK pathway-altered	*FGFR1*, *BRAF*
Diffuse midline glioma, H3 K27-altered	H3 K27, *TP53*, *PDGFRA*
Diffuse hemispheric glioma, H3 G34-mutant	H3 G34, *TP53*, *ATRX*
Diffuse pediatric-type high-grade glioma, H3-wildtype, and IDH-wildtype	IDH-wildtype, H3-wildtype, *PDGFRA*, *MYCN*, *EGFR*
Infant-type hemispheric glioma	NTRK family, *ALK*, *ROS*, *MET*
Pilocytic astrocytoma	*KIAA1549-BRAF*, *BRAF*, *NF1*
High-grade astrocytoma with piloid features	*BRAF*, *NF1*, *ATRX*
Pleomorphic xanthoastrocytoma	*BRAF*, *CDKN2A/B*
Subependymal giant cell astrocytoma	*TSC1*, *TSC2*
Ganglion cell tumors	*BRAF*
Dysembryoplastic neuroepithelial tumor	*FGFR1*
Rosette-forming glioneuronal tumor	*FGFR1*, *PIK3CA*, *NF1*
Diffuse leptomeningeal glioneuronal tumor	*KIAA1549-BRAF* fusion
Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)	*PTEN*
Extraventricular neurocytoma	FGFR (*FGFR1-TACC1* fusion), IDH-wildtype
Spinal ependymomas	*NF2*, *MYCN*
Medulloblastoma, WNT-activated	*CTNNB1*
Medulloblastoma, SHH-activated	*TP53*, *PTCH1*, *SUFU*, *SMO*, *MYCN*
Medulloblastoma, non-WNT/non-SHH	*MYC*, *MYCN*
Atypical teratoid/rhabdoid tumor	*SMARCB1*, *SMARCA4*
Desmoplastic myxoid tumor of the pineal region, *SMARCB1*-mutant	*SMARCB1*
Meningiomas	*NF2*, *SMO*, H3K27, *TERT* promoter, *CDKN2A/B*
Adamantinomatous craniopharyngioma	*CTNNB1*
Papillary craniopharyngioma	*BRAF*

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