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ΠΛΗΡΟΦΟΡΙΕΣ

Εξεταζόμενος	-	**Ημ. Συλλογής Δείγμ.**	-
ΑΜΚΑ	-	**Παραπέμπων**	-
Ημερ. Γέννησης	-	**Barcode**	26xxxxxxGR
Τύπος Δείγμ. #1	ΠΛΑΣΜΑ	**Ημερ. Παρ. Δειγμ.**	-
Τύπος Δείγμ. #2	-	**Ημερ. Αποτελ.**	-
Κωδικός Δείγμ. #1	-	**Τύπος όγκου**	ΧΟΛΑΓΓΕΙΟΚΑΡΚΙΝΩΜΑ

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Αποτελέσματα και ερμηνεία*

Βιοδείκτης	Αποτέλεσμα	Θεραπείες με ισχυρή κλινική σημασία		Θεραπείες με πιθανή κλινική σημασία	Θεραπείες με πιθανή αντίσταση
		Εγκεκριμένες/ βάσει οδηγιών θεραπείες για την ένδειξη (Level A)	Θεραπείες σε ισχυρές μελέτες (Level B)	Εκτός ένδειξης θεραπείες (Level C)	
KRAS	Exon 3 p.Q61H VAF: 0.6%	-	-	Avutometinib+Defactinib	-
Μικροδορυφορική Αστάθεια (MSI)	χωρίς μικροδορυφορική αστάθεια (MSS)	-	-	-	-

*Σημείωση: Το επίπεδο σημαντικότητας των παραλλαγών (Level of Evidence, LoE) (π.χ. A, B, C κλπ) βασίζονται στις οδηγίες για την αναφορά γενετικών παραλλαγών στον καρκίνο που δόθηκαν με κοινή συναίνεση των AMP, ACMG, ASCO και CAP. Για λεπτομερή περιγραφή των οδηγιών αυτών, ανατρέξτε στην Εικόνα 1.

-

Γιώργος Νασιούλας, PhD Μοριακός Βιολόγος, Επιστημονικός Διευθυντής, ΑΜΚΑ:26025301255

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SAMPLE INFORMATION			
Name	-	**Date Sp. Extracted**	
ID/Medical ID	-	**Req. Physician**	-
Date of Birth	-	**Report No**	26xxxxxGR
Material #1	PLASMA	**Date Received**	-
Material #2	-	**Date of Report**	-
Sample #1 ID	-	**Tumor type**	CHOLANGIOCARCINOMA

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1. Clinically Significant Biomarkers*

Biomarker	Result	Therapies with strong clinical significance		Therapies with potential significance	Therapies with potential resistance
		Approved/ Standard of care therapies (Level A)	Therapies in well powered studies (Level B)	Off label/ Investigational therapies (Level C)	
KRAS	Exon 3 p.Q61H VAF: 0.6%	-	-	Avutometinib+Defactinib	-
Microsatellite Instability (MSI)	Stable (MSS)	-	-	-	-

*Note: Variants' Level of Evidence (LoE) (e.g. A, B, C etc) are based on the Joint consensus recommendation of AMP, ACMG, ASCO and CAP for reporting genetic variants in cancer. For a detailed description of the recommendation please refer to Fig. 1

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

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Name	-	Report No	26xxxxxxGR

2. Methodology

NGS analysis

ctDNA analysis was performed using plasma-extracted cfDNA. The MagMAX Cell-Free DNA Isolation Kit (Thermofischer Scientific) was used for cfDNA. A capture based targeted next generation sequencing (NGS) analysis was performed, using the Oncology 188-Gene Variant Assay (GenePlus) which is a qualitative test which enables the simultaneous detection of single nucleotide variants (SNVs), insertions and deletions (InDels), fusions and copy number variations (CNVs) as well as microsatellite instability (MSI) in a single workflow.

Sequencing was carried out on the DNBSEQ-T7 NGS platform (MGI). The analysis of 14 genes includes the entire exon regions and CNVs of 5 genes, partial exon regions of 9 genes and introns/promoters/fusion breakpoint regions of 7 genes. The test also reports on Microsatellite Instability (MSI) status.

Sequencing data are analyzed through bioinformatics pipeline for variant calling and interpretation using the Gene+Box data analysis and management system. Alteration- and tumor type-specific therapeutic implications are classified using the OncoKB™ Levels of Evidence system, which assigns clinical actionability to individual mutational events. For additional details about the OncoKB™ curation process, please refer to the version-controlled OncoKB™ Curation Standard Operating Procedure.

Genes Analyzed

14 Gene Alterations									
BRAF*	CDKN2A*	CTNNB1	ERBB2*	IDH1	IDH2	KRAS	MET	NF1	PTEN*
TERT	TSC1	TSC2	TP53*						
7 Fusion Genes									
FGFR1	FGFR2	FGFR3	NTRK1	NTRK2	NTRK3	RET			
MSI									

*CNV (amplification/deletion) analysis is included for these genes

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 95%.

Specificity: Negative reference standards are tested with the assay, and the negative percent agreement (NPA) of SNVs, Indels, fusions and CNVs was 99%.

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 30ng cfDNA input for library preparation.

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The performance characteristics of the assay are summarized in the following table:

Variant Type	Limit of Detection
Single nucleotide variations (SNV)	VAF ≥0.2%
Insertions/deletions (Indel)	VAF ≥0.2%
Fusion (or rearrangement)	VAF ≥0.5%
Copy number (CNV)	≥2.4 copies

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. The medication information provided only on the basis of genetic test results, and the actual medication should follow the physician's instructions.
3. The clinical trials only present partial relevant clinical recruitment trials. For more comprehensive and updated information, please refer to the website: https://clinicaltrials.gov/.
4. As evidence on variants and drugs evolves, previous classifications may later be modified. The interpretation of a variant is based on current available evidence.
5. 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).
6. 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).

Limitations

1. The test is limited to test genomic variations on DNA level and does not involve RNA level or protein level.
2. Limited cell free tumor DNA (ctDNA) amount could result in false negative results.
3. 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.
4. 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.
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.

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3. Quality Control Results

Quality Control Index		Result	Criterion
Sequencing Quality Assessment	Average effective sequencing depth[1]	**12653**	≥10000
	Fraction of target covered with ≥500x[2]	100%	≥90%
	Fraction of base quality ≥Q30[3]	99%	≥80%
Overall Assessment[4]		Pass	

Note

1. Average effective sequencing depth: Average sequencing depth on target without duplicated reads.
2. Fraction of target covered with ≥ 500x: The proportion of bases that sequencing depth reach or above 500x 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 reaches or above Q30, that is the probability of base recognition accuracy rate exceeds 99.9%.
4. 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.

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4. Important biomarkers findings

Gene	Finding (VAF)	Gene	Finding (VAF)
*BRAF*_V600E	Not Detected	*NTRK1/2/3* rearrangement	Not Detected
ERBB2 amplification	Not Detected	*MSI* status	**MSS**
FGFR2 rearrangement	Not Detected	*RET* rearrangement	Not Detected
IDH1 mutation	Not Detected		

5. Immune Checkpoint inhibitors biomarkers

Biomarker/Variant	Result	Clinical Interpretation
Treatment effect - positive correlation		
MSI status	MSS	-
TP53 mutation	Not Detected	-
Treatment effect - negative correlation		
ALK rearrangement	Not Detected	-
PTEN inactivating mutation	Not Detected	-

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Name	-	Report No	26xxxxxxGR

6. Interpretations for targeted therapies

Genetic Variation:	*KRAS*: c.183A>C (p.Q61H)	VAF*: 0.6%	OncoKB

Treatment Information

Avutometinib is an inhibitor of Ras-Raf-MEK-ERK signaling being developed as a potential treatment for cancer. Defactinib is a small-molecule, oral focal adhesion kinase (FAK) inhibitor. It works by blocking FAK, a tyrosine kinase involved in cell adhesion and signaling pathways, including RAS/MEK/ERK and PI3K/Akt. Defactinib has been studied in various clinical trials for its potential anti-tumor and anti-angiogenic activities. In 2025 FDA approved defactinib in combination with avutometinib for the treatment of adult patients with recurrent low-grade serous ovarian cancer. A phase I clinical trial of RMC-6236 in patients with advanced refractory solid cancers harboring specific KRAS mutations is ongoing (NCT05379985). Setidegrasib, formerly known as ASP3082, is a first-in-class KRAS G12D-targeted protein degrader. Unlike traditional inhibitors that block protein activity, setidegrasib tags the mutant KRAS G12D protein for destruction, effectively removing the oncogenic driver from cancer cells and showing promise in treating pancreatic and non-small cell lung cancers.

Daraxonrasib is an investigational drug for cancers with RAS mutations, including Cholangiocarcinoma with KRAS G12 mutations, and it is not yet FDA-approved. In early trials, it showed a 38% overall response rate in patients with RAS-mutant NSCLC, with a median response duration of 15.1 months. It is being investigated in Phase 3 trials against docetaxel for patients with previously treated, RAS-mutant NSCLC. There are promising clinical data in patients with non-small cell lung cancer with a KRAS G12 mutation treated with the pan-RAS targeted inhibitor daraxonrasib. To date, most efforts to treat cancers with RAS mutations (with the exception of G12C), have focused on targeting downstream effectors of mutant RAS, such as RAF, MEK, or PI3K, each of which is druggable. MEK inhibitors have been the most widely investigated, typically as a combination therapy, despite the presence of multiple inhibitors that are being explored to target different KRAS-activated pathways (PMID: 33402199). The most common MEK inhibitors used in clinical practice are cobimetinib, binimetinib and trametinib. Cobimetinib is a kinase inhibitor, approved by the FDA, for use in combination with vemurafenib for the treatment of advanced melanoma with a BRAF V600E or V600K mutation (IMspire150, NCT02908672). An initial phase Ib study (NCT01988896) was conducted to investigate the safety and efficacy of cobimetinib plus atezolizumab for patients with solid tumors, 28 NSCLC patients included. Atezolizumab plus cobimetinib had manageable safety and clinical activity irrespective of KRAS/BRAF status (PMID: 30918950). Binimetinib is a potent and selective oral mitogen-activated protein kinase 1/2 (MEK 1/2) inhibitor, which is approved by the FDA in combination with encorafenib for patients with unresectable or metastatic melanoma with the BRAF V600E or V600K mutations (COLUMBUS; NCT01909453). The MEK inhibitor binimetinib has been examined in a number of clinical trials for patients with KRAS-mutated lung cancer, including studies looking at the agent in combination with chemotherapy (NCT02185690 PMID: 34052705 NCT02964689-completed/results non posted) and with palbociclib (NCT03170206-ongoing). Trametinib is a kinase inhibitor, approved by the FDA, for the treatment of melanoma, non-small cell lung cancer, thyroid cancer, and solid tumors with BRAF V600 mutations (METRIC study). The efficacy of MEK inhibitor trametinib, alone or in combination with docetaxel, has been evaluated in KRAS-mutant NSCLC. Trametinib plus docetaxel had encouraging results. Trametinib is being examined with the PD-1 inhibitor pembrolizumab in the phase Ib/II IM-BATTLE-2 trial (NCT03225664).

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Gene information

KRAS is a member of the RAS family of small GTPases, which catalyze the hydrolysis of GTP to GDP. Under physiologic conditions, these RAS proteins cycle between an active (GTP-bound) and an inactive (GDP-bound) state, to activate the MAPK and PI3K oncogenic pathway signaling downstream of Receptor Tyrosine Kinases (RTKs) (PMID: 22189424). The function of RAS enzymes is regulated by guanine nucleotide exchange factors (GEFs), such as SOS, which enable the exchange of GDP to GTP, as well as by GTPase activating proteins, such as NF1, which increase the ability of RAS to hydrolyze GTP. Once activated, RAS mediates the regulation of cellular proliferation and other cellular functions through the activation of distinct intracellular signaling pathways, including the RAF/MEK/ERK and PI3K/AKT/mTOR pathways. Transforming mutations in KRAS are frequently found in pancreatic, colon, endometrial, ovarian and biliary cancers; almost all of these mutations result in constitutive activation of KRAS, thereby promoting cell proliferation (PMID: 21993244, 24651010). KRAS mutations occur primarily in three major hotspots, G12, G13 and Q61, the first two of which occur in the GTP-ase domain and the latter interferes with the ability of NF1 to bind and regulate KRAS (PMID: 22589270, 21993244, 24651010). Other less well-characterized mutations such as A146T/V/P and L19F have also been characterized and found to be activating albeit at lower frequencies (PMID: 20147967, 20432530, 20570890). Germline KRAS mutations are responsible for both Noonan syndrome (NS) and cardio-facio-cutaneous (CFC) syndrome (PMID: 16474405, 16474404, 19467855, 17056636) that are associated with hyperactivated MAPK pathway, distinctive clinical characteristics and a predisposition to cancer (PMID: 19467855, 17704260).

Variant Information

KRAS Q61H is a hotspot mutation in a GTP binding region that increases cell colony formation, basal activation of RAS, and expression of genes involved in cytoskeletal remodeling (PMID: 20147967). This variant has less intrinsic GTPase activity than wild-type KRAS, thus maintaining KRAS in a GTP-bound, constitutively active state that promotes cell growth and other pro-survival pathways (PMID: 8524100).

Avutometinib+Defactinib DrugBank

Avutometinib, a RAF/MEK clamp inhibitor, and defactinib, a FAK inhibitor, are FDA-approved in combination for the treatment of adult patients with KRAS-mutated recurrent low-grade serous ovarian cancer (LGSOC) who have received prior systemic therapy. FDA approval was based on the results of the Phase II RAMP-201 (NCT04625270) trial of avutometinib plus defactinib in 109 patients with recurrent LGSOC.

In the Phase II RAMP-201 (NCT04625270) trial, patients with KRAS-mutated LGSOC (n=57) demonstrated an overall response rate (ORR) of 44% (n=25), with a 2% (n=2) complete response (CR) rate, 40% (n=23) partial response (PR) rate and 49% (n=28) stable disease (SD) rate, a median duration of response (DOR) of 31.0 months (95% CI=14.8-31.1) and a median progression-free survival (PFS) of 22.0 months (95% CI=11.1-36.6) (PMID: 40644648). Responders included patients with the following KRAS mutations: KRAS A146V, G12D, G12R, G12V and Q61H (PMID: 40644648). Of patients with KRAS wildtype LGSOC (n=52), the cohort demonstrated an ORR of 17% (n=9), with a 17% (n=9) PR rate and 65% (n=34) SD rate, and a median PFS of 9.2 months (95% CI=5.5-NE) (PMID: 40644648).

*VAF: Variant Allele Frequency

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Name	-	Report No	26xxxxxxGR

7. Clinical Trials to consider

KRAS associated clinical trials

NCT05874414	PHASE1 | PHASE2
Title	Combination of GNS561 and Trametinib in Patients With Advanced KRAS Mutated Cholangiocarcinoma
Treatment	GNS561 + Trametinib
Location	Puerto Rico, United States

Press here for a live search of clinical trials for KRAS

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8. Appendix

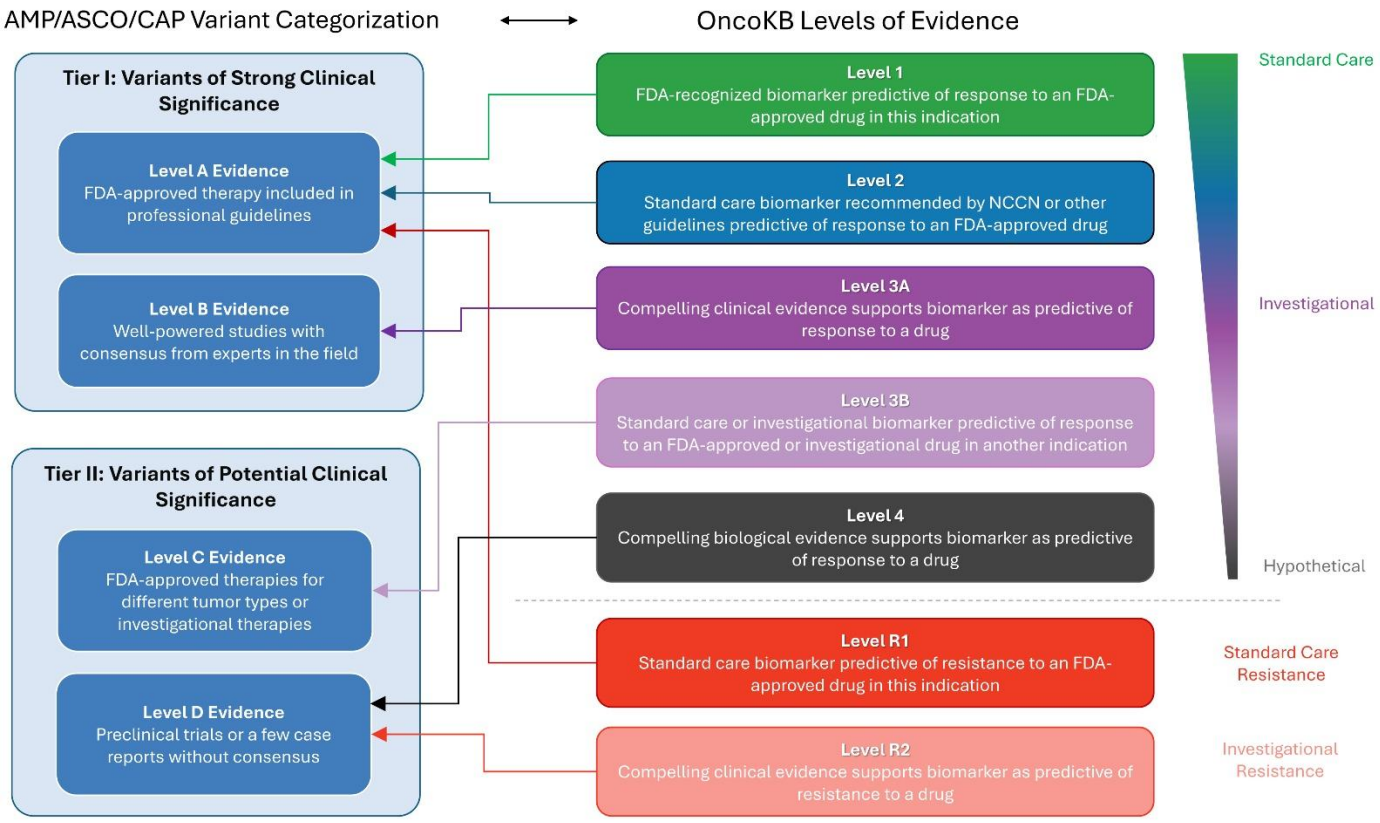

Figure 1. Joint consensus recommendation of AMP, ACMG, ASCO and CAP for reporting genetic variants in cancer. [1-2]

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Microsatellite Instability (MSI)

Microsatellite instability (MSI) is a condition of genetic hypermutability resulting from impaired DNA mismatch repair (MMR) mechanisms. It is characterized by the accumulation of mutations in short repetitive DNA sequences known as microsatellites. MSI-H is found across multiple cancer types, most notably in colorectal, endometrial, gastric, and ovarian cancer. It can arise sporadically or as part of Lynch syndrome, a hereditary condition caused by germline mutations in MMR genes (MLH1, MSH2, MSH6, PMS2).

The results of MSI are divided into three types: MSI-H, which means microsatellites are highly unstable; MSS, which means microsatellites are stable; MSI-U, which means that the sample does not meet the MSI evaluation conditions (tissues or pleural fluid samples may not have passed the MSI indicator calculation quality control due to the low DNA and/or content of tumor cells).

Pembrolizumab has received full FDA approval for adult and pediatric patients with unresectable or metastatic MSI-H or dMMR solid tumors (PMID: 35680043, 33264544) — representing the first full approval for an immunotherapy based on a predictive biomarker, regardless of solid tumor type. This approval applies to patients who have progressed after prior treatment and have no satisfactory alternative options. Beyond the tumor-agnostic indication, specific approvals have been granted for tumor types such as endometrial and colorectal cancer.

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9. Biomarker findings across all Levels of evidence (A-D)

Biomarker	Result	Therapies with strong clinical significance		Therapies with potential significance		Therapies with potential resistance
		Approved/ Standard of care therapies (Level A)	Therapies in well powered studies (Level B)	Off label/ Investigational therapies (Level C)	Therapies in pre-clinical trials (Level D)	
KRAS	Exon 3 c.183A>C (p.Q61H) VAF: 0.6%	-	-	Avutometinib+Defactinib	Trametinib Cobimetinib Binimetinib	-

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