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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**	-

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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)	
TP53	Exon 8 p.R273C VAF: 2%	-	-	-	-
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.

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-

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**	26xxxxxxGR
Material #1	PLASMA	**Date Received**	-
Material #2	-	**Date of Report**	-
Sample #1 ID	-	**Tumor type**	Prostate Cancer

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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)	
TP53	Exon 8 p.R273C VAF: 2%	-	-	-	-
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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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 30 genes includes the entire exon regions and CNVs of 11 genes, partial exon regions of 19 genes and introns/promoters/fusion breakpoint regions of 9 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

30 Gene Alterations									
AR	ATM*	ATR	BARD1	BRAF	BRCA1*	BRCA2*	BRIP1	CDK12	CHEK1
CHEK2	ERBB2*	FANCA	FANCL	FOXA1	MLH1*	MRE11	MSH2*	MSH6*	NBN
PALB2*	PMS2	PTEN*	RAD51B	RAD51C	RAD51D	RAD54L	RB1*	SPOP	TP53*
9 Fusion Genes									
ALK	FGFR1	FGFR2	FGFR3	NTRK1	NTRK2	NTRK3	RET	ROS1	
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]	**18970**	≥10000
	Fraction of target covered with ≥500x[2]	100%	≥90%
	Fraction of base quality ≥Q30[3]	98%	≥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 reach 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)
ATM mutation	Not Detected	*FANCL* mutation	Not Detected
ATR mutation	Not Detected	*MLH1* mutation	Not Detected
BARD1 mutation	Not Detected	*MRE11* mutation	Not Detected
*BRAF*_V600E	Not Detected	*MSI* status	**MSS**
BRCA1 mutation	Not Detected	*NBN* mutation	Not Detected
BRCA2 mutation	Not Detected	*NTRK1/2/3* rearrangement	Not Detected
BRIP1 mutation	Not Detected	*PABL2* mutation	Not Detected
CDK12 mutation	Not Detected	*RAD51B* mutation	Not Detected
CHEK1 mutation	Not Detected	*RAD51C* mutation	Not Detected
CHEK2 mutation	Not Detected	*RAD51D* mutation	Not Detected
ERBB2 amplification	Not Detected	*RAD54L* mutation	Not Detected
FANCA mutation	Not Detected	*RET* rearrangement	Not Detected

5. Immune Checkpoint inhibitors biomarkers

Biomarker/Variant	Result	Clinical Interpretation
Treatment effect - positive correlation		
MSI status	MSS	-
MLH1 suspected germline deleterious mutation	Not Detected	-
MSH2 suspected germline deleterious mutation	Not Detected	-
MSH6 suspected germline deleterious mutation	Not Detected	-
PMS2 suspected germline deleterious mutation	Not Detected	-
KRAS mutation	Not Detected	-
ATM mutation	Not Detected	-
ATR mutation	Not Detected	-
BRCA1 mutation	Not Detected	-
BRCA2 mutation	Not Detected	-
BRIP1 mutation	Not Detected	-
CHEK1 mutation	Not Detected	-
CHEK2 mutation	Not Detected	-
FANCA mutation	Not Detected	-
MRE11A mutation	Not Detected	-
NBN mutation	Not Detected	-

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RAD51B mutation	Not Detected	-
RAD51D mutation	Not Detected	-
RAD54L mutation	Not Detected	-
TP53 mutation	**Detected**	**May increase the benefit rate of PD-1/PD-L1 inhibitors**
Treatment effect - negative correlation		
ALK rearrangement	Not Detected	-
PTEN inactivating mutation	Not Detected	-

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6. Interpretations for targeted therapies

Genetic Variation:	*TP53*: c.817C>T (p.R273C)	VAF*: 2%	OncoKB

Gene information

TP53 encodes the p53 tumor suppressor protein, a transcription factor that responds to cellular stresses, including DNA damage and oncogenic activation, by inducing downstream anti-tumor responses such as DNA repair and apoptosis (PMID: 11099028). p53 levels are kept low in healthy cells due to negative regulation by MDM2/4, Cop1 and Trim24 and constant degradation by the ubiquitin-proteasome system (PMID: 36859359, 36207426). When DNA is damaged, a network of pathways is activated to detect and repair lesions in a cell- and context-specific manner (PMID: 36207426). p53 is rapidly phosphorylated by upstream regulators such as ATM, ATR, and CHL1/2, which results in the accumulation of stable p53 (PMID: 36207426). p53 then binds to specific DNA sequences to direct the expression of a wide variety of genes, including those involved in apoptosis, cell cycle arrest, DNA repair, senescence, stem cell differentiation, autophagy, cellular metabolism, and others (PMID: 27141080, 36859359, 36207426). Oncogenic mutations of TP53 often result in the dysregulation of p53 function, usually due to structural changes in the DNA binding domain (PMID: 36859359). Loss of p53 function can have various outcomes including tumorigenesis, invasion and metastasis, drug resistance, metabolic reprogramming, immune evasion and overall genomic instability (PMID: 36859359). TP53 is the most commonly mutated gene in human cancers, and germline mutations occur in the cancer predisposition syndrome Li-Fraumeni (PMID: 22713868, 21765642). Clinical and preclinical research into drugs that target TP53 is ongoing, notably with MDM2 inhibitors that aim to restore p53 function and are being tested in combination with other cancer therapies (PMID: 36859359, 37818252).

Variant Information

The TP53 R273C mutation is likely oncogenic. The TP53 R273C mutation is located in the protein's DNA binding domain. Expression of this mutant in TP53 null mouse embryonic fibrobalsts (MEFs) resulted in a significant increase in cell migration relative to TP53 null cells (PMID: 23612969). Structural studies demonstrated that the R273C mutation leads to a dramatic reduction in the DNA binding affinity of p53, although the protein retains wildtype stability (PMID: 23863845, 11900253). Expression of this mutation in cell lines that lack TP53 expression did not enhance TP53-mediated transcriptional activity in reporter assays, as compared to expression of wildtype TP53 (PMID: 15037740). Yet, there are no FDA-approved or NCCN-compendium listed treatments specifically for patients with TP53 R273C mutant prostate cancer.

*VAF: Variant Allele Frequency

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7. Clinical Trials to consider

TP53 associated clinical trials

NCT06739395	PHASE2
Title	Precision Medicine Trial Based on Molecular Matching Therapy for Patients With Standard Treatment Exhaustion
Treatment	Olaparib tablet | Temozolomide capsule | Anlotinib | Trametinib tablet | Dabrafenib | Vebreltinib Enteric Capsules | Alpelisib Pill | Sacituzumab Govitecan-Hziy 180 MG | Lenvatinib Capsules | Pazopanib Pill | Palbociclib Pill | Chidamide | PD-1/PD-L1/PD-1&CTLA4 inhibitor | Target Gene
Location	China

NCT06329206	PHASE1
Title	A Phase Ia/Ib Study of GH2616 Tablet in Subjects With Advanced Solid Tumors
Treatment	GH2616 Tablets
Location	China

Press here for a live search of clinical trials for TP53

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8. Appendix

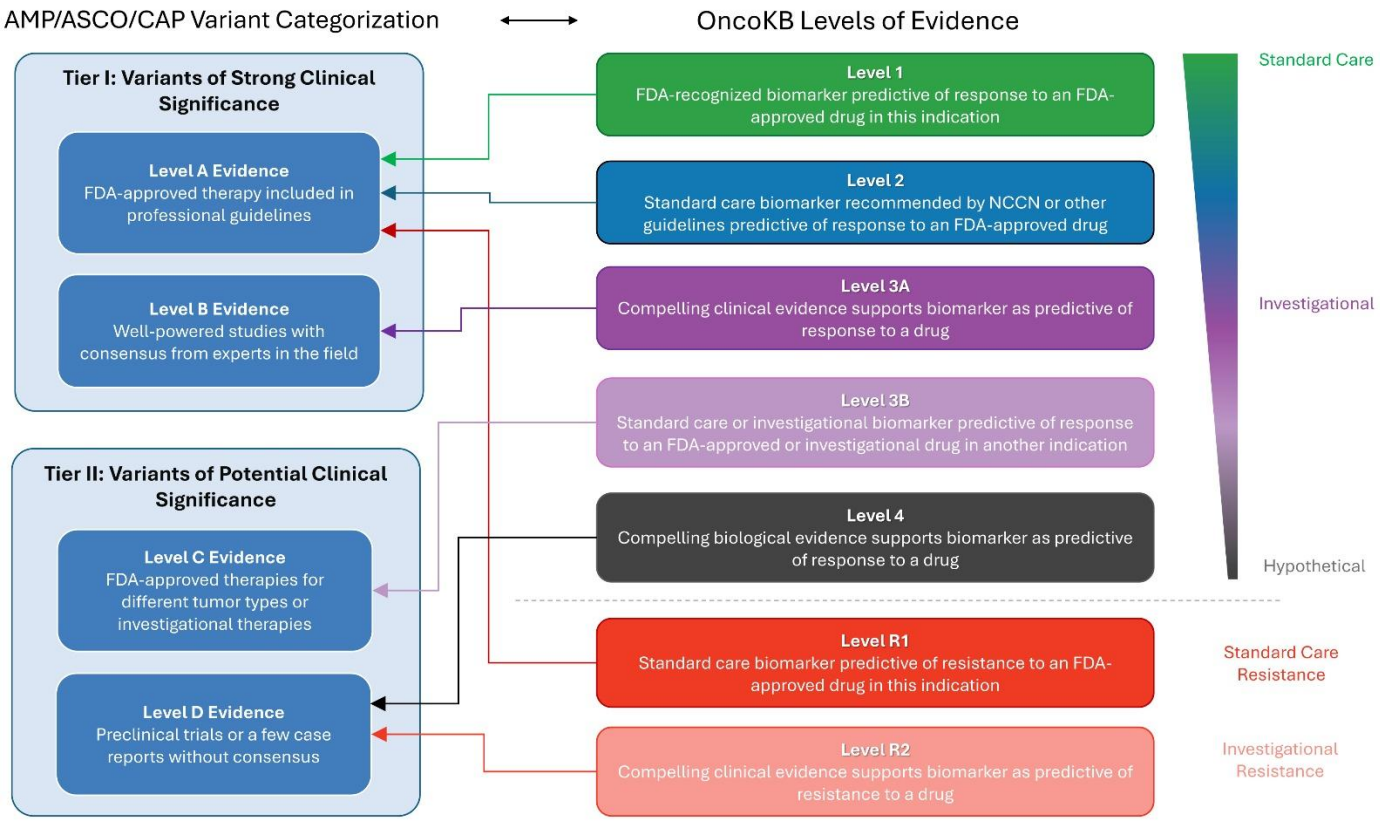

Figure 1. Joint consensus recommendation of AMP, ACMG, ASCO and CAP for reporting genetic variants in cancer. [1-2]

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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)	
TP53	Exon 8 p.R273C c.817C>T VAF: 2%	-	-	-	-	-

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