

ΠΛΗΡΟΦΟΡΙΕΣ

Εξεταζόμενος	-	Ημ. Συλλογής Δείγμ.	-
ΑΜΚΑ	-	Παραπέμπων	-
Ημερ. Γέννησης	-	Report No	26xxxxxxGR
Τύπος Δείγμ. #1	ΙΣΤΟΣ ΕΓΚΛΕΙΣΜΕΝΟΣ ΣΕ ΜΠΛΟΚ ΠΑΡΑΦΙΝΗΣ	Ημερ. Παρ. Δειγμ.	-
Τύπος Δείγμ. #2	-	Ημερ. Αποτελ.	-
Κωδικός Δείγμ. #1	-	Τύπος όγκου	ΚΑΡΚΙΝΟΣ ΩΟΘΗΚΩΝ

primeDX - 1021 Unique Genes (38 DNA level fusions) plus RNAexome analysis

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)	
ARID1A	Exon 18 p.M1481Rfs*15 VAF: 53.9%	-	-	-	-
TP53	Exon 10 p.R342Efs*3 VAF: 53.9%	-	-	-	-
Μικροδορυφορική Αστάθεια (MSI)	Χωρίς μικροδορυφορική αστάθεια (MSS)	-	-	-	-
Συνολικό Φορτίο Μεταλλαγών του όγκου (TMB)	4.5 Muts/MB	-	-	-	-
BRCA1	Δεν ανιχνεύθηκε παθολόγος μεταλλαγή στον καρκινικό ιστό	-	-	-	-
BRCA2	Δεν ανιχνεύθηκε παθολόγος μεταλλαγή στον καρκινικό ιστό	-	-	-	-
Genomic Instability Score (GIS)	Χαμηλό (26)	-	-	-	-
Ανοσοϊστοχημικοί Βιοδείκτες					
Έκφραση PD-L1 (Πίνακας S2)	CPS<1	-	-	-	-
Έκφραση ERBB2 (IHC) (Πίνακας S1)	Αρνητικό (Score 0)	-	-	-	-
FOLR1 (FRα) έκφραση (IHC)	Αρνητικό (<75%) (30%)	-	-	-	-
Ανάλυση RNA Exome					



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Δεν ανιχνεύτηκε αναδιάταξη	-	-	-	-
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*Σημείωση: Το επίπεδο σημαντικότητας των παραλλαγών (Level of Evidence, LoE) (π.χ. A, B, C, D 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.

^ Η ανάλυση συγκεκριμένων βιοδεικτών του παρόντος πολυγονιδιακού πάνελ πραγματοποιείται στο πλαίσιο διαπίστευσης κατά ΕΛΟΤ EN ISO 15189:2022 (βλ. ενότητα «Methodology»). Η διαπίστευση κατά ΕΛΟΤ EN ISO 15189:2022 αφορά αποκλειστικά τον αναλυτικό προσδιορισμό των εν λόγω βιοδεικτών. Οι ερμηνείες που σχετίζονται με την πρόβλεψη ανταπόκρισης σε θεραπεία δεν περιλαμβάνονται στο πεδίο διαπίστευσης.

Ο υπολογισμός της κατάστασης HRD βασίζεται στον συνδυαστικό έλεγχο της γενωμικής αστάθειας (GIS score) και της ανάλυσης των γονιδίων BRCA1/2 στον καρκινικό ιστό.

HRD status	GIS ¹ score	BRCA1/2 στον καρκινικό ιστό
HRD αρνητικό	Χαμηλό (26)	Αρνητικό

¹ GIS: Genomic Instability Score (LOH+LST+TAI)



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Μια εταιρεία πιστοποιημένη με ISO 9001:2015 (Cert. No 041150049) και ISO/IEC 27001:2022 (Cert. No 048190009)

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Κωδικός Εγγράφου: Δ21_PrimeDX



SAMPLE INFORMATION

Name	-	Date Sp. Extracted	-
ID/Medical ID	-	Req. Physician	-
Date of Birth	-	Report No	26xxxxxxGR
Material #1	PARAFFIN EMBEDDED TISSUE-BLOCK	Date Received	-
Material #2	-	Date of Report	-
Sample #1 ID	-	Tumor type	OVARIAN 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)	
ARID1A	Exon 18 p.M1481Rfs*15 VAF: 53.9%	-	-	-	-
TP53	Exon 10 p.R342Efs*3 VAF: 53.9%	-	-	-	-
Microsatellite Instability (MSI)	Stable (MSS)	-	-	-	-
Tumor Mutational Burden (TMB)	4.5 Muts/MB	-	-	-	-
BRCA1	No known pathogenic mutation was identified in the patient's tumor tissue	-	-	-	-
BRCA2	No known pathogenic mutation was identified in the patient's tumor tissue	-	-	-	-
Genomic Instability Score (GIS)	Low (26)	-	-	-	-
Immunohistochemistry Biomarkers					
PD-L1 expression (Table S2)	CPS<1	-	-	-	-
HER2 expression (IHC) (Table S1)	Negative (Score 0)	-	-	-	-
FOLR1 (FRα) expression (IHC)	Negative (<75%) (30%)	-	-	-	-



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RNA Exome analysis				
No fusions detected	-	-	-	-

*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

^ The analysis of selected biomarkers included in the present multigene panel is performed within the scope of accreditation according to ELOT EN ISO 15189:2022 (see «Methodology» section). Accreditation according to ELOT EN ISO 15189:2022 applies exclusively to the analytical determination of the selected biomarkers. Interpretations related to the prediction of therapeutic response are not included in the scope of accreditation.

The computation of HRD status is based on the combined test of the GIS score and the mutation analysis of BRCA1/2 genes in the cancer tissue.

HRD status	GIS ¹ score	BRCA1/2 status in tumor tissue
HRD negative	Low (26)	Negative

¹ GIS: Genomic Instability Score (LOH+LST+TAI)



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1. [Clinically Significant Biomarkers](#)
2. [Methodology](#)
3. [Quality Control Results](#)
4. [Important biomarkers findings](#)
5. [Immune Checkpoint inhibitors biomarkers](#)
6. [Interpretations for targeted therapies](#)
7. [Interpretation of findings related with chemotherapy drugs](#)
8. [Other Genomic findings](#)
9. [Variants of Uncertain Significance \(VUS\)](#)
10. [Suspected Germline variants](#)
11. [HLA-I Polymorphism variation](#)
12. [Clinical Trials to consider](#)
13. [Appendix](#)
 - a. [Immune checkpoint inhibitors predictive biomarkers](#)
 - b. [Genomic Instability](#)
 - c. [Other Immunohistochemistry Biomarkers](#)
 - d. [Genes Analyzed](#)
 - e. [Levels of Evidence for Genomic Biomarkers](#)
14. [Biomarker findings across all Levels of evidence \(A-D\)](#)
15. [References](#)



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2. Methodology

NGS analysis

DNA was extracted from the sample under investigation using the QIAamp DNA FFPE Tissue kit (QIAGEN). 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 that detects variants in 1021 tumor-related genes and gene rearrangements / fusions in 38 genes. Sequencing was carried out on an MGI sequencing platform (DNBSEQ-T7). The analysis includes the entire exon regions of 312 genes, introns/promoters/fusion breakpoint regions of 38 genes and partial coding exons of 709 genes. The test also reports 30+ immune response biomarkers, including Tumor Mutational Burden (TMB) score and 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.

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%.

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

RNA Exome

Total RNA was extracted from the submitted specimen using the RNeasy FFPE Kit (Qiagen) and evaluated for quantity and integrity. An RNA-to-cDNA conversion protocol (Nanodigmbio) was then applied, followed by cDNA library construction and hybrid-capture enrichment of all exonic and selected intronic regions of genes associated with clinically significant fusion findings. This design enables





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the detection of known and novel gene fusions involving approximately 20,000 genes, across a wide range of malignancies. Sequencing was performed on the NGS DNBSEQ-T7 platform (MGI).

Raw sequencing data were processed and analyzed using the CE-IVD commercial software SeqPilot, Version 4.4 Build 505 (JSI Medical Systems), which performs alignment to the human reference genome (GRCh37/hg19) and automated detection of gene fusions. Detected fusions were annotated and interpreted using selected databases (COSMIC, OncoKB, TCGA) including assessment of their potential clinical significance. In addition, fusion detection was also performed using STAR-Fusion v1.15.1 (PMID: [31639029](#)) with default parameters. Paired-end reads were adapter and quality trimmed using Cutadapt [DOI: <https://doi.org/10.14806/ej.17.1.200>] prior to analysis. Pre-processed reads were supplied directly to STAR-Fusion which internally invoked STAR aligner v2.7.11b (PMID: [23104886](#)) for genome alignment, configured for chimeric detection with a maximum intron size of 100 kb, splice junction overhang ≥ 10 , and a minimum chimeric segment length of 12 nt. Reads were aligned to the hg19/GRCh37 RefSeq primary assembly (GCF_000001405.25) using the corresponding RefSeq GTF for splice junction annotation. A CTAT Genome Resource Library (Mar-2021 release), built from the same genome and GTF using the prep_genome_lib.pl script from STAR-Fusion, was used internally to annotate candidate fusions and filter likely artifacts. All candidate fusions were further validated and refined using FusionInspector (PMID: [37323575](#)).

Detected fusions were annotated and interpreted using selected databases (COSMIC, OncoKB, TCGA) including assessment of their potential clinical significance.

Genomic Instability Score (GIS) analysis

The Genomic instability status was assessed using the 1021 Homologous Recombination Deficiency (HRD) Assay (GenePlus). Analysis of sequencing data was conducted using the Gene+ Box (GenePlus) bioinformatics platform. GIS is enabled by three validated genomic scar metrics: (i) Loss of Heterozygosity (LOH), which indicates subchromosomal deletions resulting in the loss of one parental allele; (ii) Telomeric Allelic Imbalance (TAI), which denotes regions of allelic imbalance that extend to the telomeres without crossing the centromere; and (iii) Large-Scale State Transitions (LST), which quantify the number of chromosomal breaks between adjacent segments of ≥ 10 Mb. Genomic segments are detected and quantified using algorithms throughout the genome, with individual scores aggregated to produce the GIS score (Rediscore). The composite score functions as a surrogate marker for compromised homologous recombination repair and is employed to categorize samples based on HRD status according to an established threshold of 42 validated for clinical relevance. HRD positivity is defined by either the presence of BRCA1/2 mutations or the presence of a GIS ≥ 42 .





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ERBB2 (HER2) expression by IHC

ERBB2 staining is performed in a VENTANA BenchMark Series automated staining instrument using the ERBB2 clone 4B5, on formalin-fixed, paraffin-embedded (FFPE) tissue. The IHC test gives a score of 0 to 3+ that measures the amount of HER2 receptor protein on the surface of cancer cells. Scoring interpretation is as follows:

HER2 IHC positive (score 3+)

HER2 IHC equivocal (score 2+)

HER2 IHC negative (score 0 or 1+)

Scoring is based on the ASCO-CAP HER2 testing guidelines (PMID: [27841667](#), [37303228](#)).

For mCRC the HERACLES criteria are also used (PMID: [26449765](#)).

PD-L1 expression by IHC - CPS (22C3)

PD-L1 protein expression is determined by using Combined Positive Score (CPS), which is the number of positive cells (tumor cells with partial or complete membrane staining as well as lymphocytes and macrophages with membrane and/or cytoplasmic staining of any intensity) divided by the total number of viable tumor cells, multiplied by 100.

DAKO 22C3 (CE IVD) by IHC is a qualitative immunohistochemical assay using Monoclonal Mouse Anti-PD-L1 22C3, intended for use in the detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) tissue specimens. The specimen submitted for testing should contain at least 100 viable tumor cells to be considered adequate for evaluation. Normal tonsil tissue is used as positive control.

FOLR1 (FRα) expression by IHC

FOLR1 (FRα) staining is performed in a VENTANA BenchMark Series automated staining instrument using the FOLR1-2.1 (Ventana/Roche Diagnostics), on formalin-fixed, paraffin-embedded (FFPE) tissue. FOLR1 expression clinical cut-off is $\geq 75\%$ viable tumor cells (TC) with membrane staining at moderate (2+) and/or strong (3+) intensity levels.

Biomarkers within the scope of accreditation (ISO15189:2022)

-AKT1, BRAF, BRCA1, BRCA2, EGFR, ERBB2, KRAS, NRAS, METex14 skipping HRAS, IDH1, IDH2, KIT, PIK3CA, PDGFRA (SNV/indel detection by NGS)

-ALK, ROS1, RET, FGFR1,2,3, NTRK1,2,3, METex14 skipping (Fusion detection by NGS)

-TMB (NGS)

-GIS score (NGS)



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- PDL1 SP263 & SP142 (IHC)
- ALK (FISH)
- HER2 (IHC, FISH, DISH)

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. 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.
2. 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.
3. Fraction of base quality $\geq$ 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%.
4. 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.
5. 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	1616	≥ 500
	Fraction of target covered with ≥ 50x ²	100%	≥99%
	Fraction of base quality ≥ Q30 ³	99%	≥80%
Tumor cell content ⁴		25%	>20%
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.



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Name NADA FREIHA

Report No 26018564GR

4. Important biomarkers findings

Gene	Finding (VAF/Copy Number/Germline Mutation)	Detected Range
EGFR	Exon 18	Not detected
	Exon 19	Not detected
	Exon 20(including T790M)	Not detected
	Exon 21	Not detected
ERBB2(HER2)	Copy number gain	Not detected
	Mutation	Not detected
ALK	Rearrangement	Not detected
	Mutation	Not detected
ROS1	Rearrangement	Not detected
MET	Copy number gain	Not detected
	Exon 14 skipping	Not detected
RET	Rearrangement	Not detected
	Mutation	Not detected
BRAF	Codon 600 mutation	Not detected
KIT	Exon 9	Not detected
	Exon 11	Not detected
	Exon 13	Not detected
	Exon 17	Not detected
PDGFRA	Exon 12	Not detected
	Exon 18	Not detected
BRCA1	Mutation	Not detected
BRCA2	Mutation	Not detected
KRAS	Codon 12/13/59/61/117/146 mutation	Not detected
	Other mutations except codon 12/13/59/61/117/146	Not detected
NRAS	Codon 12/13/59/61/117/146 mutation	Not detected
	Other mutations except codon 12/13/59/61/117/146	Not detected
PIK3CA	Mutation	Not detected
FGFR2	Rearrangement	Not detected
	Mutation	Not detected
FGFR3	Rearrangement	Not detected
	Mutation	Not detected
NTRK1	Rearrangement	Not detected
NTRK2	Rearrangement	Not detected
NTRK3	Rearrangement	Not detected
IDH1	Mutation	Not detected
PTEN	Mutation	Not detected
AKT1	Mutation	Not detected
ESR1	Mutation	Not detected

Note:



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Name

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Report No26xxxxxxGR

1. 'Not detected/-' indicates the corresponding variations were not detected in this tested individual.
2. The genetic variations listed above are covered, but not limited to this list.
3. For a detailed information about listed variants, please refer to the Report Summary and the respective Interpretations sections.



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Report No

26xxxxxxGR

5. Immune Checkpoint inhibitors biomarkers

Biomarker/Variant		Result	Clinical Interpretation
Biomarkers for predicting efficacy			
Tumor mutation burden (TMB)		TMB-L 4.5	-
Microsatellite instability (MSI)		Stable (MSS)	-
Treatment effect - positive correlation			
PD-L1 amplification		Not detected	-
PBRM1 inactivating mutation (Renal clear cell carcinoma)		Not detected	-
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	-
POLE mutation (driver)		Not detected	-
POLD1 mutation (driver)		Not detected	-
Other DNA damage repair (DDR) pathway genes	ATM mutation	Not detected	-
	ATR mutation	Not detected	-
	BAP1 mutation	Not detected	-
	BLM mutation	Not detected	-
	BRCA1 mutation	Not detected	-
	BRCA2 mutation	Not detected	-
	BRIP1 mutation	Not detected	-
	CHEK1 mutation	Not detected	-
	CHEK2 mutation	Not detected	-
	ERCC3 mutation	Not detected	-
	ERCC4 mutation	Not detected	-
	ERCC5 mutation	Not detected	-
	FANCA mutation	Not detected	-
	FANCC mutation	Not detected	-
	MRE11A mutation	Not detected	-
	NBN mutation	Not detected	-
	RAD50 mutation	Not detected	-
	RAD51 mutation	Not detected	-
	RAD51B mutation	Not detected	-
	RAD51D mutation	Not detected	-



Name		Report No	
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	<i>RAD54L</i> mutation	Not detected	-
<i>TP53</i> mutation		Detected	May increase the benefit rate of PD-1/PD-L1 inhibitors
<i>KRAS</i> mutation		Not detected	-
Treatment effect - negative correlation			
<i>PTEN</i> inactivating mutation		Not detected	-
<i>JAK1</i> inactivating mutation		Not detected	-
<i>JAK2</i> inactivating mutation		Not detected	-
<i>B2M</i> inactivating mutation		Not detected	-
<i>EGFR</i> mutation (L858R/EX19del)		Not detected	-
<i>ALK</i> rearrangement		Not detected	-
<i>STK11</i> inactivating mutation		Not detected	-
<i>KEAP1</i> inactivating mutation		Not detected	-
<i>11q13</i> amplification		Not detected	-
<i>MDM2</i> amplification		Not detected	-
<i>MDM4</i> amplification		Not detected	-
<i>DNMT3A</i> inactivating mutation		Not detected	-
Indicator affecting prognosis of immune checkpoint inhibitor therapy			
HLA-I Zygosity (At least one of type A, B, C is homozygous)		Detected	May result in shorter overall survival when treated with PD-1/PD-L1 inhibitors

Note:

1. Not detected/- indicates the corresponding variation were not detected in this tested individual.
2. The interpretation of the detection results of *PBRM1* inactivating mutations is only applicable to renal clear cell carcinoma.
3. The indicators/gene clinical interpretations listed above are for reference only, and the specific decisions need to refer to professional physician instructions.
4. For a detailed interpretation, showed in Interpretation for biomarker of checkpoint inhibitor.
5. *POLE* and *POLD1* mutations are restricted to currently reported mutations that may lead to hypermutation in tumor, resulting in tumor mutation burden increase.
6. HLA-I results analyzed by the phenotypes of HLA-A, HLA-B and HLA-C loci detected from tumor samples. Due to the lack of control samples, HLA-I typing cannot be accurately analyzed and it is possible that show homozygosity because of the occurrence of HLA-LOH in the tumor tissue.



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Report No

26xxxxxGR

6. Interpretations for targeted therapies

Genetic Variation:

NM_006015.4(ARID1A): c.4442_4469del (p.M1481Rfs*15)

VAF*: 53.9%

OncoKB

Therapies:

Under investigation in [clinical trials](#)

Gene information

ARID1A, also known as BAF250A, is a member of the SWI/SNF chromatin-remodeling complex, and plays a role in altering chromatin structure for various cellular functions, including transcription, DNA synthesis and DNA repair (PMID: [25387058](#), [23208470](#)). ARID1A binds to AT-rich regions of DNA and helps recruit other members of the SWI/SNF complex, such as SMARCA and BAF complexes. Together, these complexes are involved in ATP-dependent chromatin remodeling via nucleosome displacement and thus allow for gene expression activation (PMID: [12672490](#), [10078207](#), [11073988](#)). In a mouse model of colon cancer, ARID1A loss specifically altered enhancer-mediated gene regulation (PMID: [27941798](#)). Germline mutations in ARID1A result in Coffin-Siris syndrome, which is characterized by developmental delay and coarse facial features (PMID: [11170086](#)). Additionally, ARID1A has been identified as a tumor suppressor in multiple cancer types, including gynecologic cancers, ovarian clear cell carcinomas and endometrial cancers (PMID: [21900401](#), [21590771](#), [20826764](#)).

Variant Information

ARID1A truncating mutations can produce several forms of C-terminally truncated proteins. These mutations have been found in gastric, colon, breast, and pancreatic cancer (PMID: [22009941](#)). Endogenous expression of these mutations in ovarian and endometrial cancer cell lines demonstrated that they are activating as measured by increased cell proliferation compared to the re-expression of wildtype, and in vivo loss of ARID1A in combination with a mutation in the PTEN-PIK3CA pathway resulted in the development of ovarian cancer in transgenic mouse models (PMID: [21900401](#), [24899687](#), [25625625](#)). The ARID1A M1481Rfs*15 is a truncating mutation in a tumor suppressor gene, and therefore is likely pathogenic. Laboratory data suggest that cancer cells with ARID1A loss may be sensitive to EZH2 and BET inhibitors such as tazemetostat and PLX2853, respectively.

Genetic Variation:

NM_000546.5(TP53): c.1024del (p.R342Efs*3)

VAF*: 53.9%

OncoKB

Therapies:

Under investigation in [clinical trials](#)

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



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Name

-

Report No

26xxxxxxGR

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

Truncating mutations of TP53 occur throughout the gene and lead to the production of several C-terminally truncated protein forms. These alterations are predicted to be inactivating and are associated with poor prognosis (PMID: [11900253](#), [11753428](#), [16007150](#), [21467160](#), [19336573](#)). Experimental studies have revealed that truncating mutations promote cancer cell proliferation, survival and metastasis, since ectopic expression of these mutations in melanoma cells increased cell motility and tumor formation in vivo. This was due in part to aberrant localization of truncated proteins to the mitochondria, regulating genes involved in cell survival, including CypD (PMID: [27759562](#)). The TP53 R342Efs*3 is a truncating mutation in a tumor suppressor gene, and therefore is likely Pathogenic.

*VAF: Variant Allele Frequency



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Name

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Report No

26xxxxxGR

7. Interpretation of findings related with chemotherapy drugs

Biomarkers associated with treatment response						
Drug Classes	Drug name	Gene	dbSNP	Patient's Genotype	Patient's Variant-Drug Phenotype Annotation	Evidence Level
Aromatase inhibitors	Letrozole, Anastrozole	CYP19A1	rs4646	CC	Associated with poorer response to treatment	3
	Anastrozole	ABCB1	rs2032582	AA	Associated with better response to treatment	3
Cyclophosphamide	Cyclophosphamide	XRCC1	rs25487	CC	Associated with better response to treatment	4
	Cyclophosphamide	SOD2	rs4880	AG	Associated with moderate response to treatment	3
	Cyclophosphamide+Epirubicin	GSTP1	rs1695	AG	Associated with better response to treatment	3
Methotrexate	Methotrexate	ATIC	rs4673993	TT	Associated with poorer response to treatment	2B
Pemetrexed	Pemetrexed	MTHFR	rs1801133	GG	Associated with better response to treatment	3
Platinum-Based Chemotherapy	Platinum compounds	XRCC1	rs1799782	GA	Associated with better response to treatment	3
	Carboplatin, Cisplatin, Oxaliplatin, Platinum, Platinum compounds	ERCC1	rs11615	AA	Associated with poorer response to treatment	3
	Carboplatin, Cisplatin, Oxaliplatin, Platinum, Platinum compounds	XRCC1	rs25487	CC	Associated with better response to treatment	2B
Tamoxifen	Tamoxifen	CYP19A1	rs4646	CC	Associated with poorer response to treatment of Pre-menopausal women with breast cancer, Associated with better response to treatment of Post-menopausal women with breast cancer	3
	Tamoxifen	ABCB1	rs1045642	AG	Associated with poorer response to treatment	3
Taxanes	Paclitaxel+Cisplatin	TP53	rs1042522	GG	Associated with poorer response to treatment	3
	Paclitaxel	ABCB1	rs2032582	AA	Associated with better response to treatment	3
Vinca alkaloids	Vincristine	ABCB1	rs1045642	AG	Associated with poorer response to treatment	3

Biomarkers associated with drug toxicity						
Drug Classes	Drug name	Gene	dbSNP	Patient's Genotype	Patient's Variant-Drug Phenotype Annotation	Evidence Level



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Name		Report No 26xxxxxGR				
5-Fluorouracil (5-Fu), Fluoropyrimidines	5-Fu or Capecitabine	DPYD	rs2297595	CC	Associated with increased risk of drug toxicity	1A
	5-Fu or Capecitabine	MTHFR	rs1801133	GG	Associated with decreased risk of drug toxicity	3
	5-Fu+Leucovorin or Tegafur+Leucovorin	UMPS	rs1801019	GG	Associated with decreased risk of drug toxicity	3
	Fluoropyrimidine-based therapy	DPYD	rs67376798	TT	Associated with decreased risk of drug toxicity	1A
	Fluoropyrimidine-based therapy	DPYD	rs55886062	AA	Associated with decreased risk of drug toxicity	1A
	Fluoropyrimidine-based therapy	DPYD	rs3918290	CC	Associated with decreased risk of drug toxicity	1A
Anthracyclines	Anthracyclines	CBR3	rs1056892	GG	Associated with increased risk of drug toxicity	3
Capecitabine	Capecitabine-Based Chemotherapy	MTHFR	rs1801131	GG	Associated with increased risk of drug toxicity	3
	Capecitabine-Based Chemotherapy	DPYD	rs2297595	CC	Associated with increased risk of drug toxicity	1A
	5-Fu or Capecitabine	MTHFR	rs1801133	GG	Associated with decreased risk of drug toxicity	3
	Capecitabine	DPYD	rs67376798	TT	Associated with decreased risk of drug toxicity	1A
	Capecitabine	DPYD	rs55886062	AA	Associated with decreased risk of drug toxicity	1A
	Capecitabine	DPYD	rs3918290	CC	Associated with decreased risk of drug toxicity	1A
Cyclophosphamide	Cyclophosphamide+Epirubicin	GSTP1	rs1695	AG	Associated with decreased risk of drug toxicity	3
Gemcitabine	Gemcitabine	CDA	rs2072671	AA	Associated with increased risk of drug toxicity	3
Irinotecan	Irinotecan	UGT1A1	rs8175347	6TA/6TA	Associated with decreased risk of drug toxicity	1A
	Irinotecan	UGT1A1	rs4148323	GG	Associated with decreased risk of drug toxicity	1B
	Irinotecan	C8orf34	rs1517114	CG	Associated with increased risk of drug toxicity	3
Methotrexate	Methotrexate	MTRR	rs1801394	AG	Associated with increased risk of drug toxicity	3
	Methotrexate	ABCB1	rs1045642	AG	Associated with moderate risk of drug toxicity	3
Platinum-Based Chemotherapy	Cisplatin	XPC	rs2228001	GT	Associated with increased risk of drug toxicity	3
	Platinum compounds	GSTP1	rs1695	AG	Associated with moderate risk of drug toxicity	3
	Cisplatin, Platinum, Platinum compounds	ERCC1	rs3212986	CC	Associated with increased risk of drug toxicity	3
	Carboplatin, Cisplatin, Oxaliplatin, Platinum, Platinum compounds	ERCC1	rs11615	AA	Associated with increased risk of drug toxicity	3

Note:



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Name

-

Report No

26xxxxxxGR

1. The level of variant-drug associations evidence is based on PharmGKB website, for more detailed information please see <http://www.pharmgkb.org/page/clinAnnLevels>. Level 1A: Annotation for a variant-drug combination in a CPIC- or medical society-endorsed pharmacogenomics guideline, or implemented at a PGRN site, or in another major health system; Level 1B: Annotation for a variant-drug combination in which the preponderance of evidence shows an association. The association must be replicated in more than one cohort with significant P-values, and, preferably with a strong effect size; Level 2A: Annotation for a variant-drug combination that qualifies for level 2B where the variant is within a VIP (Very Important Pharmacogene) as defined by PharmGKB. The variants in level 2A are in known pharmacogenes, so functional significance is more likely; Level 2B: Annotation for a variant-drug combination with moderate evidence of an association. The association must be replicated, but there may be some studies that do not show statistical significance, and/or the effect size may be small; Level 3: Annotation for a variant-drug combination based on a single significant (not yet replicated) study or annotation for a variant-drug combination evaluated in multiple studies but lacking clear evidence of an association; Level 4: Annotation based on a case report, non-significant study, or in vitro, molecular, or functional assay evidence only.
2. The variant-drug correlation relationship derived from multiple independent studies, therefore, the interpretations of the same class of drug for the tested individual may be inconsistent. The final drug instruction needs to combine with the specific clinical situation.
3. The detection results are only based on the analysis of tumor samples and lack of control, the results of some loci may be specific to tumor tissues due to factors such as loss of heterozygosity.



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Report No

26xxxxxxGR

8. Other Genomic findings

***Note:** In this section, damaging variants in genes without clinical actionability or without convincing evidence of cancer association are reported.

Genetic Variation:	RAC1: Copy number gain	VAF*: NA	OncoKB
Description RAC1 (Rac Family Small GTPase 1) encodes a GTPase which belongs to the RAS superfamily of small GTP-binding proteins, which regulates a diverse array of cellular events, including the control of cell growth, cytoskeletal reorganization, and the activation of protein kinases. RAC1 mutations have been identified in human cancers including melanoma, head and neck cancer, and prostate cancer (PMID: 27991930). A copy number gain alteration in RAC1 is identified in this case and it is considered to be likely pathogenic.			

9. Variants of Uncertain Significance (VUS)

The clinical significance of the variants listed in the below table is uncertain at this time. Until the uncertainty is resolved, these variants should not be used in clinical management decisions.

Gene	Variant	Interpretation
RAD51C	c.696A>T (p.E232D)	RAD51C (RAD51 Paralog C), a member of the RAD51 family, plays a role in homologous recombination in DNA repair and cell cycle checkpoint signaling in response to DNA damage (PMID: 21821141). Germline mutations in RAD51C are associated with Fanconi anemia-like syndrome that involves predisposition to various cancers and increases the possibility developing breast and ovarian cancers (PMID: 21821141 PMID: 31446535). A missense alteration in RAD51C, p.E232D, is identified in this case. This sequence change replaces glutamic acid, which is acidic and polar, with aspartic acid, which is acidic and polar, at codon 232 of the RAD51C protein (p.Glu232Asp). This variant is not present in population databases (gnomAD no frequency). This variant has not been reported in the literature in individuals affected with RAD51C-related conditions. ClinVar contains an entry for this variant (Variation ID: 232379). Invitae Evidence Modeling of protein sequence and biophysical properties (such as structural, functional, and spatial information, amino acid conservation, physicochemical variation, residue mobility, and thermodynamic stability) indicates that this missense variant is not expected to disrupt RAD51C protein function with a negative predictive value of 80%. In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.
JAK1	c.376G>A (p.V126M)	JAK1 (Janus Kinase 1) encodes a membrane protein of protein-tyrosine kinases (PTK), which involved in the interferon-alpha/beta/gamma pathway and is a member of the JAK/STAT signaling pathway (PMID: 15575979) and plays a role in the immune response (PMID: 31892268). Activating mutations



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Document Code: Δ21_PrimeDX



Name

-

Report No

26xxxxxxGR

		in JAK1 have been identified in T-cell neoplasms (PMID: 30079384). A missense alteration in JAK1,p.V126M, is identified in this case. This variant is of uncertain clinical significance (ACMG classification).
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Name

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Report No

26xxxxxxGR

10. Suspected Germline variants

Gene	Transcript	Exon	c.HGVS	p.HGVS	Classification
-	-	-	-	-	-

Note:

1. indicates no relevant variations were detected in this test.
2. When detected, pathogenic or likely pathogenic variants are reported. Variants of uncertain significance or variants that are benign or likely benign are not reported.
3. The somatic or germline origin of the alteration identified cannot be verified due to the absence of control sample analysis (blood or saliva).
4. Variant classification interpretation is based on ACMG (American College of Medical Genetics and Genomics) guidelines for the interpretation of germline sequence variants (PMID: [25741868](#)).

11. HLA-I Polymorphism variation

Somatic HLA-I Zygosity

The anti-tumor activity of immune checkpoint inhibitor therapy is related to CD8+ T cells. The recognition of cancer cells by CD8+ T cells is achieved by HLA-I (human leukocyte antigen class I) molecules presenting tumor antigens.

HLA alleles have the characteristics of polymorphism and codominance. HLA-I loci subdivided into HLA-A, HLA-B and HLA-C. When a patient's HLA-I is homozygous at least one locus, this patient is expected to present less and less diverse tumor neoantigens to T cells compared to patients who are heterozygous at all three loci. In two cohorts, patients with heterozygous HLA-I showed longer OS than those with homozygous alleles, cohort1: HR=1.4 (1.02-1.9), P-value=0.036; cohort2: HR=1.31 (1.03- 1.7), P-value=0.028; among 32 patients with heterozygous HLA-I but at least one locus with LOH (loss of heterozygosity), patients with HLA-I LOH have a higher survival risk (P = 0.05, HR = 1.60, 95% CI 1.03-2.43), and these patients mainly with low mutation burden (P = 0.0006, HR = 3.68, 95% CI 1.64-8.23) (PMID: [29217585](#)).

Gene	Test Content	Result
HLA-A	Zygosity	Homozygosity
HLA-B	Zygosity	Heterozygosity
HLA-C	Zygosity	Heterozygosity



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Name

-

Report No

26xxxxxxGR

12. Clinical Trials to consider

ARID1A associated clinical trials

[NCT05490472](#)

PHASE1 | PHASE2

Title	JAB-2485 Activity in Adult Patients With Advanced Solid Tumors
Treatment	JAB-2485 (Aurora A inhibitor) JAB-2485 (Aurora A inhibitor)
Location	China, United States

[NCT06617923](#)

PHASE2

Title	Study of Senaparib in Combination With Temozolomide in ARID1A Mutation Associated Ovarian Cancer
Treatment	Senaparib Temozolomide
Location	United States

[NCT04104776](#)

PHASE1 | PHASE2

Title	A Study of Tulumimostat DZR123 (CPI-0209) in Patients With Advanced Solid Tumors and Lymphomas
Treatment	Tulumimostat Enzalutamide
Location	France, Italy, Poland, South Korea, Spain, United Kingdom, United States

[NCT05950464](#)

PHASE1

Title	Testing Different Amounts of the Combination of Drugs M1774 and ZEN-3694 for the Treatment of Recurrent Ovarian and Endometrial Cancer
Treatment	BET Bromodomain Inhibitor ZEN-3694 Biopsy Procedure Biospecimen Collection Computed Tomography Magnetic Resonance Imaging Tuvusertib X-Ray Imaging
Location	United States

Press [here](#) for a live search of clinical trials for ARID1A

TP53 associated clinical trials

[NCT06739395](#)

PHASE2



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Name		Report No	26xxxxxxGR
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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Name

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Report No

26xxxxxxGR

13. Appendix

a. Immune checkpoint inhibitors predictive biomarkers

Tumor Mutation Burden (TMB)

Tumor mutation burden (TMB) refers to the number of somatic mutations in the coding region, usually indicated as the total number of somatic mutations within each MB tumor genome region. The clinical utility of TMB as a predictive biomarker for anti-PD1 immunotherapy has been established in the KEYNOTE-158 trial which led to the site-agnostic FDA-approval of pembrolizumab for metastatic/untreatable solid tumors with tissue TMB value ≥ 10 muts/MB (PMID: [32919526](#)). The results of TMB are divided into three types: TMB-H, which means high tumor mutation burden; TMB-L, which means low tumor mutation burden; TMB-U, means that the sample does not meet the TMB assessment conditions (the tissue or pleural and ascites sample may fail to pass the TMB indicator calculation quality index due to low DNA quality and/or low tumor cell content).

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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Name

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Report No

26xxxxxGR

PD-L1 expression

Table S2. PD-L1 interpretation and cut-offs.

Cancer type	Therapy	PD-L1	Cut-off	We report
Non-Small Cell Lung Cancer (NSCLC)	Anti-PD-1 [1-4]	VENTANA (SP263)	1L TPS ≥ 50% 2L TPS ≥ 1%	%TPS
	Anti-PD-L1 [5-7]	VENTANA (SP263)	2L TPS ≥ 1%	%TPS
		VENTANA (SP263)	1L TPS ≥ 50%	%TPS
		VENTANA (SP142)	1L TC ≥ 50% or IC ≥ 10%	%TC/%IC
	Anti-PD-1 + Anti-CTLA-4 [8]	VENTANA (SP263)	1L TPS ≥ 1%	%TPS
Urothelial Cancer (UC)	Anti-PD-1 [9]	Dako 22C3	1L CPS ≥ 10	CPS
	Anti-PD-1 [19]	VENTANA (SP263)	1L TC ≥ 1%	%TC
	Anti-PD-L1 [10]	VENTANA (SP142)	2L IC ≥ 5%	%IC
Triple Negative Breast Cancer (TNBC)	Anti-PD-L1 [11]	VENTANA (SP142)	1L IC ≥ 1%	%IC
	Anti-PD-1 [12] + chemotherapy	Dako 22C3	1L CPS ≥ 10	CPS
Cervical cancer	Anti-PD-1 [16]	Dako 22C3	2L CPS ≥ 1	CPS
Head and Neck Squamous Cell Carcinoma (HNSCC)	Anti-PD-1 [14,15]	Dako 22C3	1L CPS ≥ 1 2L TPS ≥ 50%	CPS and %TPS
Gastric cancer (adenocarcinoma) (HER-2 Positive)	Anti-PD-1 [13,20]	Dako 22C3	1L CPS ≥ 1	CPS
Gastric cancer (adenocarcinoma) (HER-2 Negative)	Anti-PD-1 [18, 20]	Dako 22C3	1L CPS ≥ 5	CPS
Oesophageal (Adenocarcinoma and squamous carcinoma)	Anti-PD-1 [17]	Dako 22C3	1L CPS ≥ 10	CPS
Oesophageal (squamous carcinoma)	Anti-PD-1 [17]	Dako 22C3	1L TC ≥ 1%	%TC
Oesophageal (Adenocarcinoma) (HER-2 Negative)	Anti-PD-1 [17]	Dako 22C3	1L CPS ≥ 5	CPS
Gastro-oesophageal junction Adenocarcinoma (HER-2 Negative)	Anti-PD-1 [17,20] *Depending on PD-L1 inhibitor	Dako 22C3	1L CPS ≥ 5 or* 1L CPS ≥ 10	CPS
Gastro-oesophageal junction Adenocarcinoma (HER-2 Positive)		Dako 22C3	1L CPS ≥ 1	

1. Reck M, et al N Engl J Med. 2016 Nov 10;375(19):1823-1833 | 2. Herbst RS, et al Lancet. 2016 Apr 9;387(10027):1540-50. | 3. Brahmer J, et al N Engl J Med. 2015 Jul 9;373(2):123-35. | 4. Borghaei H, et al N Engl J Med. 2015 Oct 22;373(17):1627-39. | 5. Antonia SJ, et al N Engl J Med. 2018 Dec 13;379(24):2342-2350. | 6. Sezer A, et al Lancet. 2021 Feb 13;397(10274):592-604. | 7. Herbst RS, et al N Engl J Med. 2020;383(14):1328-1339. | 8. Hellmann MD, et al 2019 N Engl J Med. 2019 Nov 21;381(21):2020-2031. | 9. Balar AV, et al Lancet Oncol. 2017 Nov;18(11):1483-1492. | 10. Balar AV, et al Lancet. 2017 Jan 7;389(10064):67-76. | 11. Schmid P, et al N Engl J Med. 2018 Nov 29;379(22):2108-2121. | 12. Cortes J, et al 2020 J Clin Oncol. 2020;38(suppl 15):1000. | 13. Bang YJ, et al 2019 Mar 25. doi: 10.1007/s10120-018-00909-5. | 14. Cohen EEW, et al Lancet Oncol. 2019 Jan 12;393(10167):156-167. | 15. Rischin D, et al 2019 J Clin Oncol 37, (suppl; abstr 6000) | 16. Chung HC, et al 2018 J Clin Oncol 36:15_suppl, 5522-5522 | 17. Kojima T, et al J Clin Oncol. 2020;38(35):4138-4148. | 18. Yelena Y Janjigian et al., 2021. 10.1016/S0140-6736(21)00797-2 | 19. 2021 Jun 3;384(22):2102-2114. doi: 10.1056/NEJMoa2034442.20. Yelena Y. Janjigian, et al Nature. 2021 December ; 600(7890): 727–730. doi:10.1038/s41586-021-04161-3. | 20. Yelena Y. Janjigian, et al Nature. 2021 December ; 600(7890): 727–730. doi:10.1038/s41586-021-04161-3

TPS: Tumor Proportion Score = $\frac{\text{\#PD-L1 positive tumor cells}}{\text{Total \#PD-L1 positive+PD-L1 negative tumor cells}} \times 100$

TC: tumor cell

CPS: Combined Positive Score = $\frac{\text{\#PD-L1 staining cells (tumor cells, lymphocytes, macrophages)}}{\text{Total \# of viable tumor cells}} \times 100$

IC: immune cell



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Report No

26xxxxxxGR

b. Genomic Instability

Genomic Instability Score (GIS) analysis

Homologous recombination deficiency (HRD) has emerged as a key biomarker for guiding the use of poly (ADP-ribose) polymerase inhibitors (PARPi) across multiple tumor types, most notably ovarian, breast, pancreatic, and prostate cancers. HRD encompasses both germline and somatic mutations in BRCA1/2, as well as broader genomic instability (GI) signatures that reflect impaired homologous recombination repair. This DNA repair deficiency sensitizes tumors to synthetic lethality induced by PARP inhibition (PMID: [35274707](#)).

Genomic instability is typically quantified using the Genomic Instability Score (GIS), a composite metric derived from three genomic scar markers: Loss of Heterozygosity (LOH), Large-Scale Transitions (LST), and Telomeric Allelic Imbalance (TAI). In the PAOLA-1 trial, patients with GIS-high ovarian tumors (GIS ≥ 42) experienced significantly greater clinical benefit from maintenance therapy with olaparib plus bevacizumab compared to bevacizumab alone, leading to regulatory approval of this combination for HRD-positive cases (PMID: [37761329](#), [37809048](#)).

Beyond ovarian cancer, the predictive value of HRD has been validated in multiple landmark trials. The PROfound trial in prostate cancer, OlympiAD trial in HER2-negative breast cancer, and POLO trial in metastatic pancreatic cancer all demonstrated that patients with HRD-positive tumors, defined by either BRCA mutations or GI, derive meaningful improvements in progression-free survival and treatment response when treated with PARPi agents. These include olaparib, niraparib, rucaparib, and talazoparib, which have received FDA and EMA approval across various indications (PMID: [37761329](#)). Together, these findings underscore the clinical utility of HRD testing as a predictive biomarker that enables precise patient stratification for PARPi therapy and informs personalized treatment strategies across multiple solid tumors. On October 23, 2019, the Food and Drug Administration approved niraparib for patients with advanced ovarian, fallopian tube, or primary peritoneal cancer treated with three or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD)- positive status.



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Report No

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c. Other Immunohistochemistry Biomarkers

FOLR1 (FRα)

The *FOLR1* gene encodes the Folate Receptor 1, a protein that binds folate and mediates its transport into cells. Folate is essential for DNA synthesis, repair, and methylation, making FOLR1 important for cell division and growth. Overexpression of FOLR1 has been found in various cancers, such as ovarian, lung, and breast cancers.

Based on the results of Study 0416 (MIRASOL, NCT04209855), FDA granted full approval for mirvetuximab soravtansine-gynx, for adult patients with FRα-positive, platinum-resistant epithelial ovarian, Fallopian tube, or primary peritoneal cancer, who have received 1-3 prior systemic treatment regimens.

ERBB2 (HER2) expression by IHC

ERBB2, a receptor tyrosine kinase, is altered by mutation, amplification and/or overexpression in various cancer types, most frequently in breast, esophagogastric and endometrial cancers. FDA has granted approval to several anti-ERBB2 regimens, either as single or combination therapy for various cancer types. In addition, recently FDA granted accelerated approval to fam-trastuzumab deruxtecan-nxki, for adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.

Table S3. ERBB2 Biomarkers associated with treatment response (LoE)

Cancer Type	3+ IHC	2+ IHC & ≥2 FISH	ERBB2 amplification by NGS	IHC 1+ or IHC 2+/ISH -ve
Breast Cancer	Trastuzumab Deruxtecan (1A.1)	Trastuzumab Deruxtecan (1A.1)	Trastuzumab Deruxtecan (2C.1)	Trastuzumab Deruxtecan (1A.1)
	Trastuzumab (1A.1)	Ado-Trastuzumab Emtansine (1A.1)	Trastuzumab (2C.1)	
	Ado-Trastuzumab Emtansine (1A.1)	Lapatinib + Capecitabine (1A.1)	Ado-Trastuzumab Emtansine (2C.1)	
	Lapatinib + Capecitabine (1A.1)	Lapatinib + Letrozole (1A.1)	Lapatinib + Capecitabine (2C.1)	
	Lapatinib + Letrozole (1A.1)	Margetuximab + Chemotherapy (1A.1)	Lapatinib + Letrozole (2C.1)	
	Margetuximab + Chemotherapy (1A.1)	Neratinib (1A.1)	Margetuximab + Chemotherapy (2C.1)	
	Neratinib (1A.1)	Neratinib + Capecitabine (1A.1)	Neratinib (2C.1)	
	Neratinib + Capecitabine (1A.1)	Trastuzumab + Tucatinib + Capecitabine (1A.1)	Neratinib + Capecitabine (2C.1)	
	Trastuzumab + Tucatinib + Capecitabine (1A.1)	Trastuzumab + Chemotherapy (1A.1)	Trastuzumab + Tucatinib + Capecitabine (2C.1)	
	Trastuzumab + Chemotherapy (1A.1)	Trastuzumab + Pertuzumab + Chemotherapy (1A.1)	Trastuzumab + Chemotherapy (2C.1)	
Colorectal Cancer	Trastuzumab Deruxtecan (1A.1)	Tucatinib + Trastuzumab (1A.1)	Tucatinib + Trastuzumab (1A.1) (RAS/BRAF wild type)	N/A
	Tucatinib + Trastuzumab (1A.1)	Lapatinib + Trastuzumab (1A.2)	Trastuzumab Deruxtecan (2C.1)	
	Lapatinib + Trastuzumab (1A.2)	Trastuzumab + Pertuzumab (1A.2)	Lapatinib + Trastuzumab (2C.1) (RAS/BRAF wild type)	
	Trastuzumab + Pertuzumab (1A.2)	Trastuzumab Deruxtecan (2C.1)	Trastuzumab + Pertuzumab (2C.1) (RAS/BRAF wild type)	



Name		Report No		
-		26xxxxxxGR		
Gastric/GEJ	Trastuzumab Deruxtecan (1A.1)	Pembrolizumab+ Trastuzumab + Chemotherapy (1A.1) (PD-L1 with CPS>1% required)	Pembrolizumab+ Trastuzumab + Chemotherapy (2C.1) (PD-L1 with CPS>1% required)	N/A
	Trastuzumab + Chemotherapy (1A.1)	Trastuzumab + Chemotherapy (1A.1)	Trastuzumab + Chemotherapy (2C.1)	
	Pembrolizumab + Trastuzumab + Chemotherapy (1A.1) (PD-L1 with CPS>1% required)	Trastuzumab Deruxtecan (1A.1)	Trastuzumab Deruxtecan (2C.1)	
	Zanidatamab-hrrii + Tislelizumab-jsgr + Chemotherapy (1A.1)	Zanidatamab-hrrii + Tislelizumab-jsgr + Chemotherapy (1A.1)		
	Zanidatamab-hrrii + Chemotherapy (1A.1)			
Biliary Tract	Trastuzumab Deruxtecan (1A.1)	Trastuzumab Deruxtecan (2C.1)	Trastuzumab Deruxtecan (2C.1)	N/A
	Zanidatamab-hrrii (1A.1)	Zanidatamab-hrrii (2C.1)	Zanidatamab-hrrii (2C.1)	
	Trastuzumab + Pertuzumab (1A.2)	Trastuzumab + Pertuzumab (1A.2)	Trastuzumab + Pertuzumab (2C.1)	
	Tucatinib + Trastuzumab (1A.2)	Tucatinib + Trastuzumab (1A.2)	Tucatinib + Trastuzumab (2C.1)	
Uterine Serous Carcinoma/ Papillary Serous	Trastuzumab Deruxtecan (1A.1)	Trastuzumab Deruxtecan (2C.1)	Trastuzumab Deruxtecan (2C.1)	N/A
	Trastuzumab + Carboplatin-Taxol Regimen (1A.2)	Trastuzumab + Carboplatin-Taxol Regimen (2C.1)	Trastuzumab + Carboplatin-Taxol Regimen (2C.1)	
Lung Cancer	Trastuzumab Deruxtecan (1A.1)	Trastuzumab Deruxtecan (2C.1)	Trastuzumab Deruxtecan (2C.1)	N/A
All tumors	Trastuzumab Deruxtecan (1A.1)	Trastuzumab Deruxtecan (2C.1)	Trastuzumab Deruxtecan (2C.1)	N/A



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Report No

26xxxxxxGR

d. Genes Analyzed

312 genes including all exon regions and available for detecting SNV / Indel / CNV

ABL1	ACVR1B	AKT1	AKT2	AKT3	ALK	APC	AR	ARAF	ARID1A
ARID1B	ARID2	ASXL1	ATM	ATR	ATRX	AURKA	AURKB	AXIN1	AXIN2
AXL	B2M	BAP1	BARD1	BCL2	BCL2L1	BCOR	BLM	BMPR1A	BRAF
BRCA1	BRCA2	BRD4	BRIP1	BTK	CARD11	CASP8	CBFB	CBL	CCND1
CCND2	CCND3	CCNE1	CD274	CDC73	CDH1	CDK12	CDK4	CDK6	CDK8
CDKN1A	CDKN1B	CDKN2A	CDKN2B	CDKN2C	CEBPA	CHEK1	CHEK2	CIC	CREBBP
CRKL	CSF1R	CTCF	CTNNA1	CTNNB1	CUL3	CYLD	DAXX	DDR1	DDR2
DICER1	DNMT3A	DOT1L	EGFR	EIF1AX	EMSY	EP300	EPAS1	EPCAM	EPHA2
EPHA3	EPHA5	EPHB1	EPHB6	ERBB2	ERBB3	ERBB4	ERCC1	ERCC3	ERCC4
ERCC5	ERG	ERRFI1	ESR1	EXT1	EXT2	EZH2	FAM123B	FAM175A	FANCA
FANCC	FANCD2	FANCE	FANCF	FANCG	FANCL	FANCM	FAS	FAT1	FAT2
FBXW7	FGF19	FGF3	FGF4	FGFR1	FGFR2	FGFR3	FGFR4	FH	FLCN
FLT1	FLT3	FLT4	FOXA1	FOXL2	FOXP1	FUBP1	GALNT12	GATA3	GNA11
GNAQ	GNAS	GRIN2A	GRM3	HDAC1	HGF	HNF1A	HOXB13	HRAS	IDH1
IDH2	IFNG	IFNGR1	IGF1R	IKBKE	IKZF1	IL7R	INPP4B	IRF2	IRS2
JAK1	JAK2	JAK3	JUN	KDM5A	KDM5C	KDM6A	KDR	KEAP1	KIT
KRAS	LRP1B	MAF	MAP2K1	MAP2K2	MAP2K4	MAP3K1	MAPK1	MAX	MCL1
MDM2	MDM4	MED12	MEF2B	MEN1	MET	MITF	MLH1	MLH3	MLL
MLL2	MLL3	MPL	MRE11A	MS4A1	MSH2	MSH3	MSH6	MST1R	MTOR
MUTYH	MYC	MYCL1	MYCN	MYD88	NBN	NCOR1	NF1	NF2	NFE2L2
NFKB1A	NKX2-1	NOTCH1	NOTCH2	NOTCH3	NPM1	NRAS	NSD1	NTHL1	NTRK1
NTRK2	NTRK3	PALB2	PARK2	PARP1	PAX5	PBRM1	PCK1	PDCD1	PDCD1LG2
PDGFRA	PDGFRB	PDK1	PIK3CA	PIK3CB	PIK3CG	PIK3R1	PIK3R2	PMS1	PMS2
POLD1	POLE	POT1	PPP2R1A	PRDM1	PRKAR1A	PTCH1	PTCH2	PTEN	PTPN11
PTPRD	RAC1	RAD50	RAD51	RAD51B	RAD51C	RAD51D	RAD52	RAD54L	RAF1
RARA	RB1	RBM10	RECQL	RECQL4	RET	RHOA	RICTOR	RINT1	RNF43
ROS1	RPTOR	RUNX1	SDHA	SDHAF2	SDHB	SDHC	SDHD	SERPINB3	SERPINB4
SETD2	SF3B1	SLX4	SMAD2	SMAD3	SMAD4	SMARCA4	SMARCB1	SMO	SOCS1
SOX2	SOX9	SPOP	SRC	STAG2	STAT3	STK11	SUFU	SYK	TBX3
TCF7L2	TERC	TET2	TGFBR2	TMEM127	TMPRSS2	TNFAIP3	TNFRSF14	TOP1	TOP2A
TP53	TSC1	TSC2	TSHR	U2AF1	VEGFA	VHL	WRN	WT1	XPO1
XRCC2	ZMAT3								



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38 genes including specific intron, promoter and fusion breakpoint regions and available for detecting gene rearrangement or fusion

ALK	BCL2L11	BRAF	BRCA1	BRD4	CD74	EGFR	EML4	ERG	ETV6
EZR	FGFR1	FGFR2	FGFR3	KIF5B	KIT	MAML2	MET	MSH2	MYC
MYCL1	NCOA4	NOTCH2	NTRK1	NTRK2	NTRK3	PDGFRA	RAF1	RET	ROS1
RSPO2	SDC4	SLC34A2	TERT	TFE3	TMPPSS2	TPM3	PMS2		

709 genes including partial exon regions and available for detecting SNV / Indel

ABCA13	ABCB1	ABCC1	ABCC11	ABCC2	ABCG2	ABL2	ACACA	ACIN1	ACTB
ACTG1	ACTG2	ACVR2A	ACVRL1	ADAM29	ADAMTS5	ADCY1	AFF1	AFF2	AFF3
AHNAK	AKAP9	ALB	AMOT	ANGPT1	ANK3	ANKRD11	ANKRD30A	ANKRD30B	APEX1
APOBEC3B	ARAP3	ARFGEF1	ARFGEF2	ARHGAP29	ARHGAP35	ARID4B	ARID5B	ARNT	ASCL4
ASH1L	ASMTL	ASPM	ASTN1	ASXL2	ATIC	ATP11B	ATP12A	ATP1A1	ATP2B3
BAZ2B	BBC3	BBS9	BCAS1	BCL10	BCL11A	BCL11B	BCL2A1	BCL2L11	BCL3
BCL6	BCL9	BCORL1	BCR	BIRC3	BMPR2	BNC2	BPTF	BRD2	BRD3
BRSK1	BRWD1	BTLA	BUB1	C15orf23	C15orf55	C1QA	C1S	C3orf70	C7orf53
C8orf34	CACNA1E	CADM2	CALR	CAMTA1	CASP1	CASQ2	CBLB	CBR1	CBR3
CCDC168	CCNA1	CCNB3	CCT3	CCT5	CCT6B	CD22	CD33	CD5L	CD74
CDA	CDH11	CDH18	CDH23	CDK13	CHD1	CHD1L	CHD4	CHD6	CHD8
CHD9	CHFR	CHI3L1	CHN1	CIITA	CLDN18	CLP1	CLSPN	CLTC	CNOT3
CNOT4	CNTN1	CNTN5	CNTNAP1	CNTNAP5	COL1A1	COL2A1	COL5A1	COL5A2	COL5A3
COPS2	CPS1	CRIPAK	CRLF2	CRNKL1	CRTC1	CSF1	CSF3R	CSMD1	CSMD3
CSNK1A1	CSNK1G3	CTLA4	CTNNA2	CTNND1	CUX1	CXCR4	CYBA	CYP19A1	CYP1A1
CYP1B1	CYP2A13	CYP2C8	CYP2D6	CYP3A4	CYP3A5	DCC	DDX3X	DDX5	DEK
DHX35	DHX9	DIAPH1	DIS3L2	DLC1	DMD	DNAH6	DNAJB1	DNM2	DNMT1
DNMT3B	DOCK2	DOCK7	DPYD	DRGX	DTX1	DUSP22	DYSF	E2F3	EBF1
ECT2L	EED	EEF1A1	EGFL7	EGR3	EIF2AK3	EIF2C3	EIF3A	EIF4A2	EIF4G3
ELAC2	ELF1	ELF3	ELMO1	ELN	EME2	EMID2	EML4	EPC1	EPHA1
EPHA4	EPHA7	EPHB2	EPHB4	EPOR	EPPK1	EPS15	ERBB2IP	ERCC2	ESR2
ETS1	ETV1	ETV5	ETV6	EWSR1	EZR	F8	FAM131B	FAM135B	FAM157B
FAM46C	FAM5C	FAP	FASLG	FAT3	FAT4	FCGR1A	FCGR2A	FCGR2B	FCGR3A
FCRL4	FGF10	FGF12	FGF14	FGF23	FGF6	FLG	FLI1	FLNC	FMN2
FN1	FNDC4	FOXA2	FOXO1	FOXO3	FOXQ1	FRMPD4	FUS	FXR1	FYN
FZD1	G3BP1	G3BP2	GAB2	GABRA6	GATA1	GATA2	GFRAL	GIGYF1	GKN2
GLB1L3	GLI1	GLI2	GLI3	GMPS	GNA13	GNG2	GPC3	GPR124	GPS2



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GPX1	GRB7	GSK3B	GSTM5	GSTP1	GUSB	H3F3A	H3F3B	H3F3C	HCLS1
HCN1	HDAC4	HDAC9	HECW1	HEY1	HIST1H1C	HIST1H1D	HIST1H1E	HIST1H2AC	HIST1H2AG
HIST1H2AL	HIST1H2AM	HIST1H2BC	HIST1H2BD	HIST1H2BJ	HIST1H2BK	HIST1H2BO	HIST1H3B	HIST1H3C	HIST1H3D
HIST1H3F	HIST1H3G	HIST1H3H	HIST1H3I	HIST1H4I	HIST3H3	HLA-A	HLA-B	HLA-C	HLF
HMCN1	HNF1B	HNRPD	HOXA11	HOXA13	HOXA3	HOXA9	HOXC13	HOXD11	HOXD13
HSD3B1	HSP90AA1	HSP90AB1	HSPA8	HSPD1	HSPH1	ICK	ICOSLG	ID3	IFITM3
IGF1	IGF2	IGF2R	IGLL5	IKZF2	IKZF3	IL10	IL1RAPL1	IL21R	IL6
IL6ST	IMPG1	ING1	INHBA	INPP4A	INPPL1	INSR	IRF4	IRF6	IRS1
ITGB3	ITK	ITSN1	JARID2	KALRN	KAT6A	KAT6B	KCNJ5	KCNQ2	KDM2B
KEL	KIF5B	KLF4	KLHL6	KLK1	KRTAP5-5	L3MBTL1	LAMA2	LATS1	LATS2
LCP1	LEF1	LGALS8	LIFR	LPHN2	LPP	LRP2	LRP4	LRP5	LRP6
LRRC7	LRRK2	LYN	LZTS1	MACF1	MAD1L1	MAGI2	MAML2	MAML3	MAP3K13
MAPK3	MCC	MCM3	MDC1	MECOM	MEF2C	MGA	MIB1	MIOS	MKL1
MLL4	MLLT3	MMP11	MMP2	MN1	MNDA	MNX1	MSH4	MSN	MSR1
MTHFR	MTRR	MUC5B	MYH11	MYH14	MYH9	MYO3A	MYOD1	NAP1L1	NAV3
NCAM2	NCF2	NCF4	NCK1	NCOA3	NCOA4	NCOR2	NCSTN	NDUFA13	NFATC4
NFE2L3	NKX3-1	NLRC3	NOD1	NOS3	NOTCH4	NQO1	NR1I2	NR2F2	NR4A2
NRG1	NRP2	NRXN1	NTM	NUMA1	NUP107	NUP210	NUP93	NUP98	OBSCN
OGDH	OMD	OPCML	OR11G2	OR2T4	OR4A15	OR4C6	OR5L2	OR6F1	P2RY8
P4HB	PABPC1	PABPC3	PAG1	PAK1	PAK3	PASK	PAX3	PAX7	PC
PCDH18	PCSK6	PCSK7	PDCD11	PDE4DIP	PDGFB	PDILT	PER1	PGR	PHF1
PHF6	PIK3C2A	PIK3C2B	PIK3C2G	PIK3C3	PIM1	PKD1L2	PKHD1	PLAG1	PLCB1
PLCG1	PLCG2	PLK1	PLXNA1	PLXNB2	PNRC1	POLQ	POM121	POM121L12	POU2AF1
PPM1D	PPP1R17	PPP6C	PRDM16	PREX2	PRF1	PRKAA1	PRKCB	PRKCI	PRKDC
PRRX1	PRX	PSG2	PSIP1	PSMB1	PSMB5	PTGS1	PTGS2	PTPN13	PTPN2
PTPRB	PTPRK	PTPRO	PTPRS	PTPRT	PTPRU	RAB35	RAC2	RAD21	RAD54B
RANBP2	RASA1	RASGRP1	RBL1	REL	RELN	RFC1	RGS3	RHEB	RHOH
RHOT1	RIT1	RNASEL	ROBO1	ROBO2	ROBO3	ROCK1	RPGR	RPS6KB1	RPS6KB2
RSPO2	RSPO3	RUNX1T1	RUNX2	RXRA	RYR1	RYR2	SBDS	SCUBE2	SDC4
SEC31A	SEMA3A	SEMA3E	SEMA6A	SERPINA7	SETBP1	SETDB1	SF1	SF3A1	SFPQ
SGCZ	SGK1	SH2B3	SH2D1A	SH3PXD2A	SHH	SI	SIN3A	SLC16A1	SLC1A2
SLC22A16	SLC22A18	SLC22A2	SLC22A3	SLC34A2	SLCO1B3	SLIT1	SLIT2	SMARCD1	SMARCE1
SMC1A	SMC1B	SNCAIP	SNTG1	SNX29	SOD2	SOS1	SOX10	SOX17	SPEN
SPRR3	SPSB4	SPTA1	SRD5A2	SRGAP1	SRGAP3	SRSF2	SRSF7	STAG1	STAT1



Name					Report No				
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SUCLG1	SUCLG2	SULT1A1	SUZ12	SVEP1	SYNCRIP	SYNE1	TAF1	TAF15	TAF1L
TAL1	TBL1XR1	TBX15	TBX22	TCEB1	TCF12	TCF3	TCF4	TCL1A	TEC
TENM3	TERT	TET1	TFDP1	TFDP2	TFE3	TGFBR1	THBS2	TJP1	TLE1
TLL2	TLR4	TLX3	TMEM132D	TNFSF11	TNN	TP53BP1	TP63	TP73	TPM3
TPR	TRAF2	TRAF7	TRIM24	TRIM58	TRIO	TRPC5	TRRAP	TSHZ2	TSHZ3
TTF1	TUBA3C	TUBB3	TUSC3	TXNIP	TYMS	TYR	UBE2D2	UBR5	UGT1A1
UMPS	UPF3B	USH2A	USP6	USP8	VEZF1	VIM	VTCN1	WASF3	WDR90
WDT1	WHSC1	WHSC1L1	WIPF1	WNK1	WNT5A	WSCD2	WVOX	WWP1	WWP2
XIAP	XPC	XRCC1	XRCC3	YAP1	YY1AP1	ZBTB16	ZC3H11A	ZFHX3	ZFP36L1
ZFP36L2	ZFPM2	ZIC3	ZNF217	ZNF384	ZNF521	ZNF638	ZNF750	ZNF804B	

36 HRR genes analyzed

ATM	ATR	ATRX	BAP1	BARD1	BLM	BRCA1	BRCA2	BRIP1	CDK12
CHEK1	CHEK2	C11orf30	ERCC1	FAM175A	FANCA	FANCC	FANCD2	FANCE	FANCF
FANCG	FANCL	FANCM	MRE11	NBN	PALB2	RAD50	RAD51	RAD51B	RAD51C
RAD51D	RAD52	RAD54L	RECQL	RECQL4	WRN				



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e. Levels of Evidence for Genomic Biomarkers

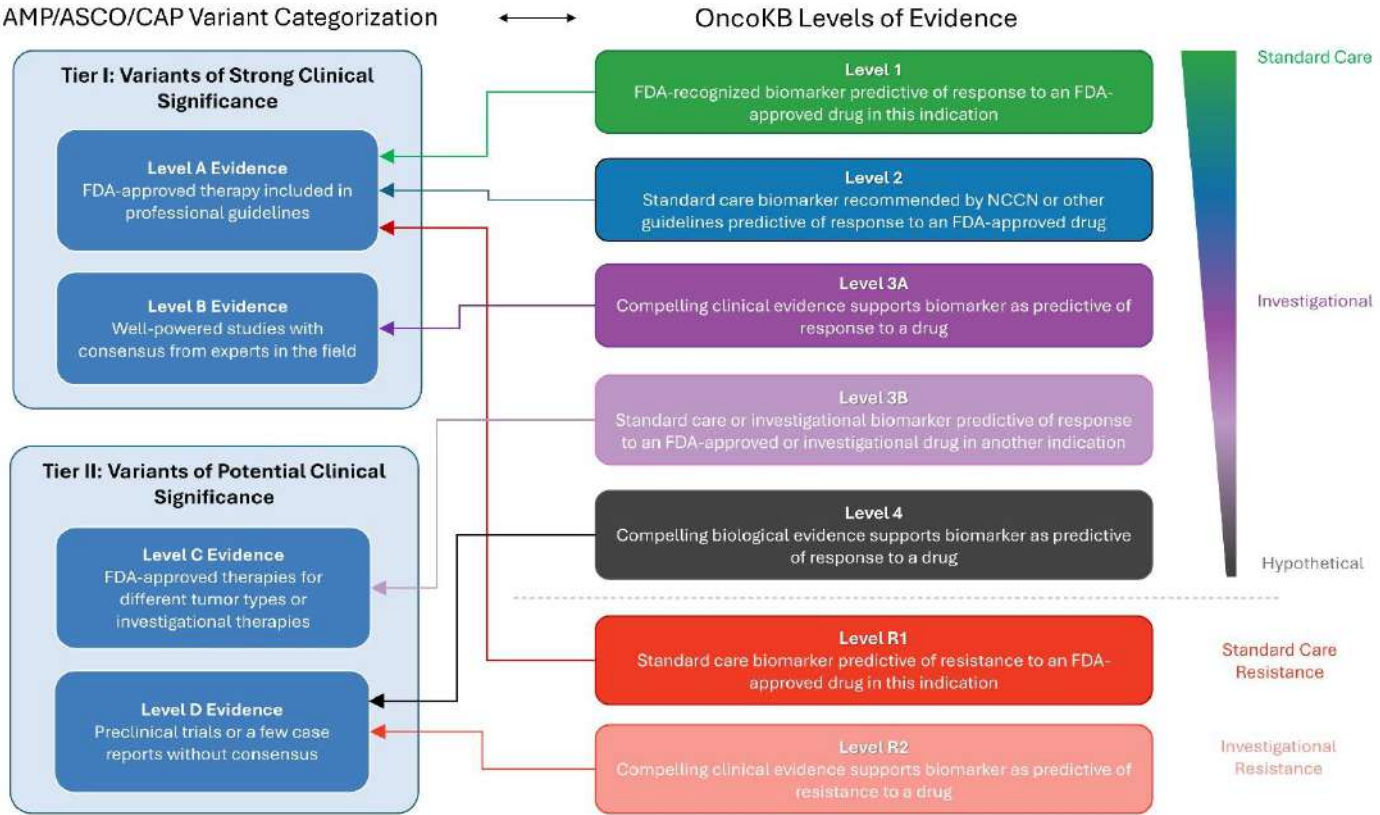


Figure 1. Joint consensus recommendation of AMP, ACMG, ASCO and CAP for reporting genetic variants in cancer. [1-2]

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14. 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)	
ARID1A	Exon 18 c.4442_4469del (p.M1481Rfs*15)) VAF: 53.9%	-	-	-	Tazemetostat Zavabresib	-
TP53	Exon 10 c.1024del (p.R342Efs*3) VAF: 53.9%	-	-	-	-	-



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