prime DX
PRECISION INDIVIDUALIZED MEDICINE

**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 |

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

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

| 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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## 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 ≥2%; Non-hotspot: VAF ≥5% |
| Insertions/deletions (Indel) | Hotspot: VAF ≥2%; Non-hotspot: VAF ≥5% |
| Fusion (or rearrangement) | VAF ≥2% |



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**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 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 ≥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)

-PDL1 SP263 & SP142 (IHC)



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-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 ≥ 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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## 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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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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## 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 | - |

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|---|---|---|
| *RAD54L* mutation | Not detected | - |
| *TP53* mutation | **Detected** | May increase the benefit rate of PD-1/PD-L1 inhibitors |
| *KRAS* mutation | Not detected | - |
| **Treatment effect - negative correlation** | | |
| *PTEN* inactivating mutation | Not detected | - |
| *JAK1* inactivating mutation | Not detected | - |
| *JAK2* inactivating mutation | Not detected | - |
| *B2M* inactivating mutation | Not detected | - |
| *EGFR* mutation (L858R/EX19del) | Not detected | - |
| *ALK* rearrangement | Not detected | - |
| *STK11* inactivating mutation | Not detected | - |
| *KEAP1* inactivating mutation | Not detected | - |
| *11q13* amplification | Not detected | - |
| *MDM2* amplification | Not detected | - |
| *MDM4* amplification | Not detected | - |
| *DNMT3A* inactivating mutation | Not detected | - |
| **Indicator affecting prognosis of immune checkpoint inhibitor therapy** | | |
| HLA-I Zygosity<br>(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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## 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/SWF 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 often result in the dysregulation of p53 function, usually due to structural changes in the DNA binding domain (PMID: 36859359). Loss

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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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## 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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|---|---|---|---|---|---|---|
| **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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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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## 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 |
|---|---|---|---|

**Descritpion**

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: 21821141PMID: 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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| | | |
|---|---|---|
| | | 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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## 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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## 12. 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

### 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 |

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| NCT04104776 | PHASE1 \| PHASE2 |
|---|---|
| **Title** | A Study of Tulmimetostat DZR123 (CPI-0209) in Patients With Advanced Solid Tumors and Lymphomas |
| **Treatment** | Tulmimetostat \| 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

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## 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≥10muts/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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**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%<br>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<br>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]<br>*Depending on PD-L1 inhibitor | Dako 22C3 | 1L CPS ≥ 5 or*<br>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 = $\frac{\#PD-L1 \text{ positive tumor cells}}{Total\ \#PD-L1\ positive+PD-L1\ negative\ tumor\ cells} \times 100$

**TC**: tumor cell

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

**IC**: immune cell

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## 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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## 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-ERRB2 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)<br>Trastuzumab (1A.1)<br>Ado-Trastuzumab Emtansine (1A.1)<br>Lapatinib + Capecitabine (1A.1)<br>Lapatinib + Letrozole (1A.1)<br>Margetuximab + Chemotherapy (1A.1)<br>Neratinib (1A.1)<br>Neratinib + Capecitabine (1A.1)<br>Trastuzumab + Tucatinib + Capecitabine (1A.1)<br>Trastuzumab + Chemotherapy (1A.1)<br>Trastuzumab + Pertuzumab + Chemotherapy (1A.1) | Trastuzumab Deruxtecan (1A.1)<br>Ado-Trastuzumab Emtansine (1A.1)<br>Lapatinib + Capecitabine (1A.1)<br>Lapatinib + Letrozole (1A.1)<br>Margetuximab + Chemotherapy (1A.1)<br>Neratinib (1A.1)<br>Neratinib + Capecitabine (1A.1)<br>Trastuzumab + Tucatinib + Capecitabine (1A.1)<br>Trastuzumab + Chemotherapy (1A.1)<br>Trastuzumab + Pertuzumab + Chemotherapy (1A.1)<br>Trastuzumab (2C.1) | Trastuzumab Deruxtecan (2C.1)<br>Trastuzumab (2C.1)<br>Ado-Trastuzumab Emtansine (2C.1)<br>Lapatinib + Capecitabine (2C.1)<br>Lapatinib + Letrozole (2C.1)<br>Margetuximab + Chemotherapy (2C.1)<br>Neratinib (2C.1)<br>Neratinib + Capecitabine (2C.1)<br>Trastuzumab + Tucatinib + Capecitabine (2C.1)<br>Trastuzumab + Chemotherapy (2C.1)<br>Trastuzumab + Pertuzumab + Chemotherapy (2C.1) | Trastuzumab Deruxtecan (1A.1) |
| **Colorectal Cancer** | Trastuzumab Deruxtecan (1A.1)<br>Tucatinib + Trastuzumab (1A.1)<br>Lapatinib + Trastuzumab (1A.2)<br>Trastuzumab + Pertuzumab (1A.2) | Tucatinib + Trastuzumab (1A.1)<br>Lapatinib + Trastuzumab (1A.2)<br>Trastuzumab + Pertuzumab (1A.2)<br>Trastuzumab Deruxtecan (2C.1) | Tucatinib + Trastuzumab (1A.1) *(RAS/BRAF wild type)*<br>Trastuzumab Deruxtecan (2C.1)<br>Lapatinib + Trastuzumab (2C.1) *(RAS/BRAF wild type)*<br>Trastuzumab + Pertuzumab (2C.1) *(RAS/BRAF wild type)* | N/A |



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| **Gastric/GEJ** | Trastuzumab Deruxtecan (1A.1)<br>Trastuzumab + Chemotherapy (1A.1)<br>Pembrolizumab + Trastuzumab + Chemotherapy (1A.1) *(PD-L1 with CPS>1% required)* | Pembrolizumab+ Trastuzumab + Chemotherapy (1A.1) *(PD-L1 with CPS>1% required)*<br>Trastuzumab + Chemotherapy (1A.1)<br>Trastuzumab Deruxtecan (1A.1) | Pembrolizumab+ Trastuzumab + Chemotherapy (2C.1) *(PD-L1 with CPS>1% required)*<br>Trastuzumab + Chemotherapy (2C.1)<br>Trastuzumab Deruxtecan (2C.1) | N/A |
| **Billiary Tract** | Trastuzumab Deruxtecan (1A.1)<br>Zanidatamab-hrii (1A.1)<br>Trastuzumab + Pertuzumab (1A.2)<br>Tucatinib + Trastuzumab (1A.2) | Trastuzumab Deruxtecan (2C.1)<br>Zanidatamab-hrii (2C.1)<br>Trastuzumab + Pertuzumab (1A.2)<br>Tucatinib + Trastuzumab (1A.2) | Trastuzumab Deruxtecan (2C.1)<br>Zanidatamab-hrii (2C.1)<br>Trastuzumab + Pertuzumab (2C.1)<br>Tucatinib + Trastuzumab (2C.1) | N/A |
| **Uterine Serous Carcinoma/ Papillary Serous** | Trastuzumab Deruxtecan (1A.1)<br>Trastuzumab + Carboplatin-Taxol Regimen (1A.2) | Trastuzumab Deruxtecan (2C.1)<br>Trastuzumab + Carboplatin-Taxol Regimen (2C.1) | Trastuzumab Deruxtecan (2C.1)<br>Trastuzumab + Carboplatin-Taxol Regimen (2C.1) | N/A |
| **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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## 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 | TMPRSS2 | 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 | HNRPDL | 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 |



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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 |
| WDTC1 | WHSC1 | WHSC1L1 | WIPF1 | WNK1 | WNT5A | WSCD2 | WWOX | 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

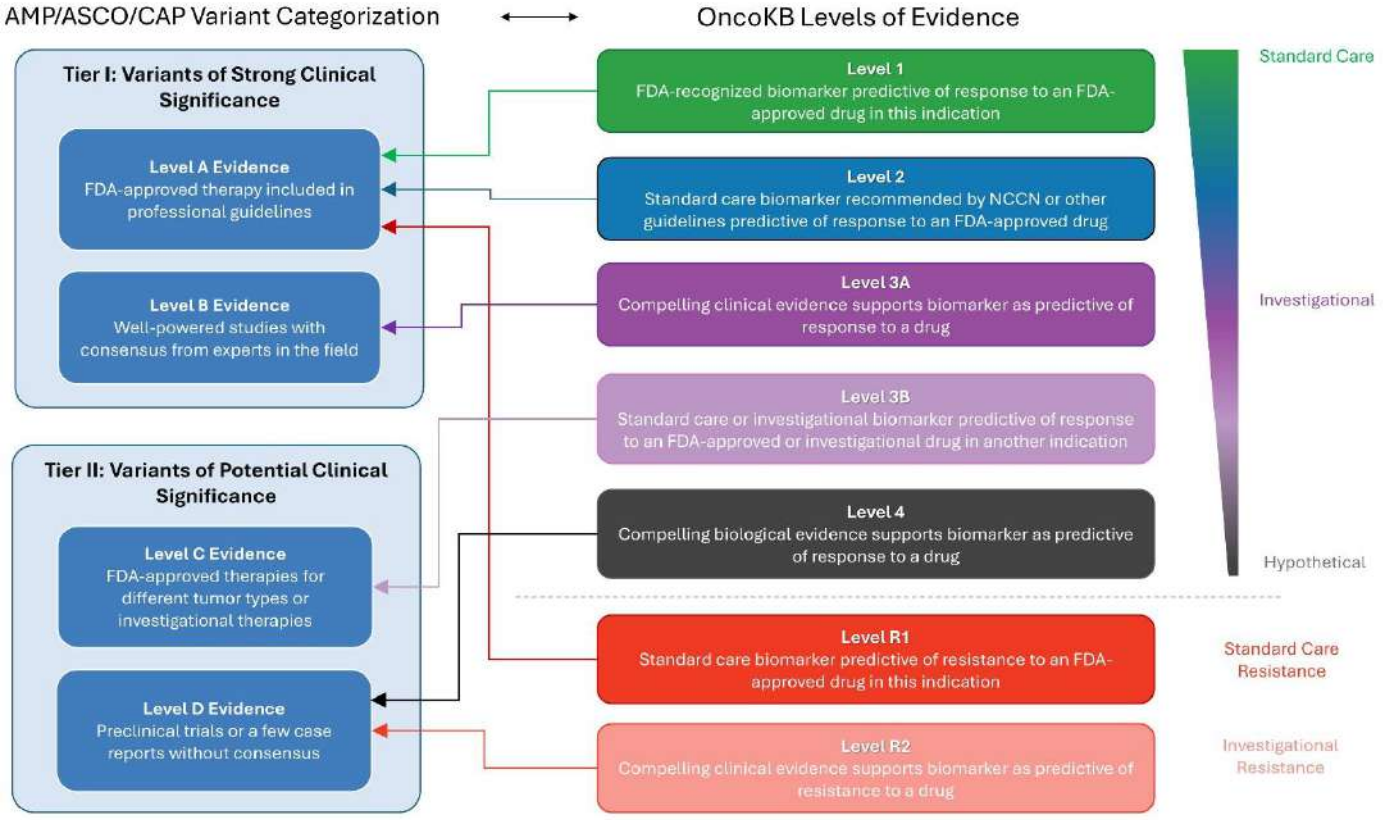


**Figure 1.** Joint consensus recommendation of AMP, ACMG, ASCO and CAP for reporting genetic variants in cancer. [1-2]

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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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