

ΠΛΗΡΟΦΟΡΙΕΣ

Εξεταζόμενος:		Ημ. Συλλογής Δείγμ.:	
ΑΜΚΑ:		Παραπέμπων:	
Ημερ. Γέννησης:		Report No:	
Τύπος Δείγμ. #1:	ΠΛΑΣΜΑ	Ημερ. Παρ. Δειγμ.:	
Τύπος Δείγμ. #2:		Ημερ. Αποτελ.:	
Κωδικός Δείγμ. #1		Τύπος όγκου:	ΚΑΡΚΙΝΟΣ ΠΡΟΣΤΑΤΗ

primeDX

1. Περίληψη έκθεσης αποτελέσματος

1021	Γονίδια (38 αναδιατάξεις) αναλύθηκαν	1	Κλινικά σημαντικές γενωμικές αλλοιώσεις που ανιχνεύθηκαν
3	Εγκεκριμένες θεραπείες που σχετίζονται με Βιοδείκτες για την ένδειξη	1	Θεραπίες με πιθανό όφελος που σχετίζονται με Βιοδείκτες
0	Θεραπίες με πιθανή αντίσταση που σχετίζονται με Βιοδείκτες	15	Κλινικές μελέτες που σχετίζονται με Βιοδείκτες

2. Βιοδείκτες με κλινική σημασία*

Βιοδείκτης	Αποτέλεσμα	Εγκεκριμένες θεραπείες για την ένδειξη	Θεραπίες με πιθανό όφελος	Θεραπίες με πιθανή αντίσταση/τοξικότητα	Κλινικές μελέτες
BRCA2	Exon 11 c.6141delT (p.Tyr2047Ter)	Olaparib (1A.1) Rucaparib (1A.1) Talazoparib+Enzalutamide (1A.1)	Niraparib (2C.1)	-	ναι
Μικροδορυφορική Αστάθεια (MSI)	χωρίς μικροδορυφορική αστάθεια (MSS)	-	-	-	-
Συνολικό Φορτίο Μεταλλαγών του όγκου (TMB)	1.88 Muts/MB	-	-	-	-

*Σημείωση: Το επίπεδο σημαντικότητας των παραλλαγών (Level of Evidence, LoE) (π.χ. 1A.1, 2C.1, 1B κλπ) βασίζονται στις οδηγίες για την αναφορά γενετικών παραλλαγών στον καρκίνο που δόθηκαν με κοινή συναίνεση των AMP, ACMG, ASCO και CAP. Για λεπτομερή περιγραφή των οδηγιών αυτών, ανατρέξτε στην Εικόνα 1.



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SAMPLE INFORMATION

Name: **Date Sp. Extracted:**
Medical ID: **Req. Physician:**
Date Of Birth: **Report No:**
Material #1: PLASMA **Date Received:**
Material #2: **Date Of Report:**
Sample #1 ID: **Tumor type:** PROSTATE CANCER

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1. Report Summary

1021 Unique Genes (38 Fusions) analyzed	1 Clinically significant biomarkers identified
3 Biomarker related approved therapies for indication	1 Biomarker related therapies with potential benefit
0 Biomarker related therapies with potential resistance	15 Biomarker related Clinical Trials

2. Clinically Significant Biomarkers*

Biomarker	Result	Approved therapies for indication	Therapies with potential benefit	Therapies with potential resistance/toxicity	Clinical Trials
BRCA2	Exon 11 c.6141delT (p.Tyr2047Ter)	Olaparib (1A.1) Rucaparib (1A.1) Talazoparib+Enzalutamide (1A.1)	Niraparib (2C.1)	-	yes
Microsatellite Instability (MSI)	Stable (MSS)	-	-	-	-
Tumor Mutational Burden (TMB)	1.88 Muts/MB	-	-	-	-

*Note: Variants' Level of Evidence (LoE) (e.g. 1A.1, 2C.1, 1B etc) are based on the Joint consensus recommendation of AMP, ACMG, ASCO and CAP for reporting genetic variants in cancer. For a detailed description of the recommendation please refer to Fig. 1



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3. Important biomarkers findings

Gene	Detected Range	Finding (VAF/Copy Number/Germline Mutation)
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
ESR1	Mutation	Not detected
ALK	Rearrangement	Not detected
ROS1	Rearrangement	Not detected
MET	Copy number gain	Not detected
	Exon 14 skipping	Not detected
RET	Rearrangement	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	c.6141delT (p.Tyr2047Ter)
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

Note:

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



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4. Immune Checkpoint inhibitors biomarkers

Biomarker/Variant		Result	Clinical Interpretation
Biomarkers for predicting efficacy			
Tumor mutation burden (TMB)		TMB-L 1.88	-
Microsatellite instability (MSI)		Stable (MSS)	-
Affect the treatment effect - positive correlation			
PD-L1 amplification		Not detected	-
PBRM1 inactivating mutation Renal clear cell carcinoma)		Not detected	-
MLH1 germline deleterious mutation		Not detected	-
MSH2 germline deleterious mutation		Not detected	-
MSH6 germline deleterious mutation		Not detected	-
PMS2 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	-	
RAD54L mutation	Not detected	-	
TP53 mutation		Not detected	-



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Biomarker/Variant	Result	Clinical Interpretation
<i>KRAS</i> mutation	Not detected	-
Affect the 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)	Not detected	-

Note:

- Not detected/- indicates the corresponding variation were not detected in this tested individual.
- The interpretation of the detection results of *PBRM1* inactivating mutations is only applicable to renal clear cell carcinoma.
- The indicators/gene clinical interpretations listed above are for reference only, and the specific decisions need to refer to professional physician instructions.
- For a detailed interpretation, showed in Interpretation for biomarker of checkpoint inhibitor.
- POLE* and *POLD1* mutations are restricted to currently reported mutations that may lead to hypermutation in tumor, resulting in tumor mutation burden increase.
- 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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5. Interpretations for targeted therapies

Genetic Variation:	<i>NM_000059.3 (BRCA2): c.6141delT (p.Tyr2047Ter)</i>	VAF:49%	OncoKB	CIVIC	COSMIC
Therapies:	Olaparib, Rucaparib, Talazoparib+Enzalutamide (1A.1), Niraparib (2C.1)				

Gene Description

BRCA2 (breast cancer susceptibility gene 2) is a tumor suppressor gene that functions as a DNA repair protein. BRCA2 has been implicated in regulating diverse cellular processes including transcription, cell cycle regulation, and DNA damage response, with a particularly important role in DNA repair during homologous recombination (PMID: 22193408). BRCA2 forms protein complexes with known tumor suppressors including RAD51, BRCA1, and PALB2; specifically, BRCA2 binds single-stranded DNA and loads RAD51 monomers at sites of DNA double-strand breaks (PMID: 28976962). RAD51 requires the BRCA1-BRCA2-PALB2 complex to initiate homologous recombination (PMID: 11239455). BRCA2 is a tumor suppressor protein; if one copy of the gene is inactivated in the germline, the result is hereditary breast and ovarian cancer (HBOC) syndrome, an autosomal dominant disease (PMID: 15800615). BRCA2 was also identified as a definitive Fanconi anemia susceptibility gene that results from biallelic mutations in the gene (PMID: 12065746). Germline BRCA2 mutations confer a 50-60% lifetime risk of breast cancer, a 30% lifetime risk of ovarian cancer, a 20-fold increased risk of prostate cancer, and a risk for the development of a broad range of cancers (PMID: 31343663).

Variant Description

This sequence change results in a premature translational stop signal in the BRCA2 gene. It is expected to result in an absent or disrupted protein product. (PMID: 20104584). This variant is not present in population databases (gnomAD no frequency). The mutation database ClinVar does not contain an entry for this variant. Loss-of-function variants in BRCA2 are known to be pathogenic. For these reasons, this variant is classified as pathogenic.

Targeted Drug Interpretation

FDA approved olaparib for adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC), who have progressed following prior treatment with enzalutamide or abiraterone. Efficacy was investigated in PROfound (NCT02987543), an open-label, multicenter trial. A statistically significant improvement was demonstrated for olaparib compared to investigator’s choice in Cohort A for rPFS with a median of 7.4 months vs 3.6 months, for OS with a median of 19.1 months vs. 14.7 months and for ORR 33% vs 2%. A statistically significant improvement for olaparib compared to investigator’s choice was also demonstrated for rPFS in Cohort A+B, with a median of 5.8 months vs. 3.5 months.

FDA approved olaparib with abiraterone and prednisone (or prednisolone) for adult patients with deleterious or suspected deleterious BRCA-mutated metastatic castration-resistant prostate cancer, as determined by an FDA-approved companion diagnostic test. Efficacy was evaluated in the PROpel trial that enrolled 796 patients with metastatic castration-resistant prostate cancer.

FDA granted accelerated approval to rucaparib for patients with deleterious BRCA mutation (germline and/or somatic)-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy. Efficacy was investigated in TRITON2 (NCT02952534), an ongoing, multi-center, single arm clinical trial in 115 patients with BRCA-mutated (germline and/or somatic) mCRPC who had been treated with androgen receptor-directed therapy and taxane-based chemotherapy. Objective response rate (ORR) and duration of response (DOR) were assessed in 62 patients with measurable disease. The



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confirmed ORR was 44% (95% CI: 31, 57). Median DOR was not evaluable (NE; 95% CI: 6.4, NE). The range for the DOR was 1.7-24+ months. Fifteen of the 27 (56%) patients with confirmed objective responses had a DOR of ≥ 6 months.

The FDA has received a new drug application for niraparib plus dual action abiraterone acetate tablets and prednisone for the treatment of patients with BRCA-positive metastatic castration-resistant prostate cancer (mCRPC) by data from the phase 3 MAGNITUDE study (NCT03748641), in which investigators evaluated the safety and efficacy of niraparib plus abiraterone for front-line mCRPC with or without homologous recombination repair (HRR) alterations. Furthermore, the FDA has granted priority review to a supplemental new drug application for the combination of talazoparib and enzalutamide for metastatic castration-resistant prostate cancer (mCRPC). The combination showed significantly improved radiographic progression-free survival (rPFS) compared to placebo and enzalutamide, according to positive results from the phase 3 TALAPRO-2 study.

Olaparib



Olaparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1, PARP2, and PARP3. PARP enzymes are involved in normal cellular homeostasis, such as DNA transcription, cell cycle regulation, and DNA repair. Olaparib has been shown to inhibit growth of select tumor cell lines in vitro and decrease tumor growth in mouse xenograft models of human cancer both as monotherapy or following platinum-based chemotherapy. Increased cytotoxicity and anti-tumor activity following treatment with olaparib were noted in cell lines and mouse tumor models with deficiencies in BRCA. In vitro studies have shown that olaparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complex, resulting in disruption of cellular homeostasis and cell death. Olaparib is available as oral tablets marketed under the brand name Lynparza.

It is indicated for the following conditions:

Ovarian cancer

- For the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy.
- In combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability.
- For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy.
- For the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.

Breast cancer

- For the treatment of adult patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor



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(HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Latest research supports the use of adjuvant olaparib in patients with high-risk early-stage HER2-negative breast cancer and germline BRCA mutations (PMID: 34081848).

Pancreatic cancer

- For the maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen.

Prostate cancer

- For the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone.

Rucaparib



Rucaparib is a potent mammalian poly(ADP-ribose) polymerase (PARP) 1, 2 and 3 inhibitor with anticancer properties. PARP is an enzyme that plays an essential role in DNA repair by activating response pathways and facilitating repair, and defects in these repair mechanisms have been demonstrated in various malignancies, including cancer. Regulation of repair pathways is critical in promoting necessary cell death. BRCA genes are tumor suppressor genes mediate several cellular process including DNA replication, transcription regulation, cell cycle checkpoints, apoptosis, chromatin structuring and homologous recombination (HR). Homologous recombination deficiency (HRD), along with PARP inhibition, is a vulnerability that enhances the cell death pathway when the single mutations alone would permit viability. Ovarian cancer commonly possesses defects in DNA repair pathways such as HRD due to BRCA mutations or otherwise. There are three main types of ovarian cancer: epithelial (90%), germ cell (5%) and sex cord stromal cell (5%). Epithelial ovarian, being the most common, fifth leading cause of cancer-related deaths in women in the United States. Advanced ovarian cancer particularly poses challenges due to reduced therapeutic response rates from standard platinum-based chemotherapy and overall survival rates. Rucaparib has shown to induce cytotoxicity in tumor cell lines with deficiencies in BRCA1/2 and other DNA repair genes. Of all the BRCA1/2 mutations in ovarian cancer, most are due to germline mutations (18%), and approximately 7% represent somatic mutations acquired within the tumor. The indication of rucaparib as an oral monotherapy in patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer was granted accelerated approval in 2016 for selected patients who have previously received greater than two lines of platinum-based therapy. It is currently marketed in the US under the brand name Rubraca that contains rucaparib camsylate as the active ingredient. It is indicated for:

Ovarian cancer

- for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.



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- for the treatment of adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies.

Prostate cancer

- for the treatment of adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy. This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Talazoparib



Talazoparib was approved by the FDA for use in germline BRCA mutated, HER2 negative, locally advanced or metastatic breast cancer on October 16, 2018 under the trade name Talzenna. Talzenna was granted approval based on the results of the EMBRACA trial in which talazoparib resulted in a mean 8.6 months progression-free survival time versus physician's choice chemotherapy which resulted in 5.6 months progression-free survival.

Talazoparib is indicated for the treatment of adult patients with deleterious or suspected deleterious germline BRCA mutated, HER2 negative locally advanced or metastatic breast cancer.

Enzalutamide



Enzalutamide is a second-generation androgen receptor inhibitor used to treat castration-resistant prostate cancer and metastatic castration-sensitive prostate cancer.

Enzalutamide is indicated for the treatment of castration-resistant prostate cancer and metastatic castration-sensitive prostate cancer (mCRPC). It is also used in combination with talazoparib for the treatment of adult patients with HRR gene-mutated mCRPC.

Niraparib



Niraparib is an orally active PARP inhibitor to treat ovarian cancer. FDA approval on March 2017. It is marketed under the brand name Zejula.

Niraparib is indicated for:

- the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy
- for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy
- for the treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with three or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either:
 - a deleterious or suspected deleterious BRCA mutation, or



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o genomic instability and who have progressed more than six months after response to the last platinum-based chemotherapy.

6. Interpretation for polymorphism variants related with chemotherapy drugs

Drug Classes	Test Content	Drug name	Gene	dbSNP	Patient's Genotype	Patient's Variant-Drug Phenotype Annotation	Evidence Level
Fluoropyrimidines	Drug efficacy	5-Fu+Oxaliplatin	<i>GSTP1</i>	rs1695	AG	Associated with moderate response to treatment	2A
	Drug toxicity	5-Fu or Capecitabine	<i>DPYD</i>	rs2297595	TT	Associated with decreased risk of drug toxicity	2A
			<i>MTHFR</i>	rs1801133	GG	Associated with decreased risk of drug toxicity	2A
		5-Fu+Leucovorin or Tegafur+Leucovorin	<i>UMPS</i>	rs1801019	GG	Associated with decreased risk of drug toxicity	2B
		Fluoropyrimidine-based therapy	<i>DPYD</i>	rs67376798	TT	Associated with decreased risk of drug toxicity	1A
			<i>DPYD</i>	rs55886062	AA	Associated with decreased risk of drug toxicity	1A
			<i>DPYD</i>	rs3918290	CC	Associated with decreased risk of drug toxicity	1A
Anthracyclines	Drug toxicity	Anthracyclines	<i>CBR3</i>	rs1056892	GG	Associated with increased risk of drug toxicity	2B
		Epirubicin	<i>GSTP1</i>	rs1695	AG	Associated with decreased risk of drug toxicity	2A
	Drug efficacy	Epirubicin	<i>GSTP1</i>	rs1695	AG	Associated with better response to treatment	2A
Aromatase inhibitors	Drug efficacy	Letrozole, Anastrozole	<i>CYP19A1</i>	rs4646	AC	Associated with better response to treatment	3
		Anastrozole	<i>ABCB1</i>	rs2032582	CC	Associated with poorer response to treatment	3
	Drug toxicity	Anastrozole	<i>ABCB1</i>	rs1045642	AG	Associated with increased risk of drug toxicity	3
Capecitabine	Drug toxicity	Capecitabine-Based Chemotherapy	<i>MTHFR</i>	rs1801131	GG	Associated with increased risk of drug toxicity	2A
		Capecitabine-Based Chemotherapy	<i>DPYD</i>	rs2297595	TT	Associated with decreased risk of drug toxicity	2A
		5-Fu or Capecitabine	<i>MTHFR</i>	rs1801133	GG	Associated with decreased risk of drug toxicity	2A
			<i>DPYD</i>	rs67376798	TT	Associated with decreased risk of drug toxicity	1A
		Capecitabine	<i>DPYD</i>	rs55886062	AA	Associated with decreased risk of drug toxicity	1A
			<i>DPYD</i>	rs3918290	CC	Associated with decreased risk of drug toxicity	1A
Cyclophosphamide	Drug toxicity	Cyclophosphamide	<i>XRCC1</i>	rs25487	CT	Associated with decreased risk of drug toxicity	3
			<i>MTHFR</i>	rs1801133	GG	Associated with decreased risk of drug toxicity	2A
		Cyclophosphamide+Epirubicin	<i>GSTP1</i>	rs1695	AG	Associated with decreased risk of drug toxicity	2A
	Drug efficacy	Cyclophosphamide	<i>XRCC1</i>	rs25487	CT	Associated with poorer response to treatment	3

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			<i>SOD2</i>	rs4880	AG	Associated with moderate response to treatment	2B
		Cyclophosphamide+Epirubicin	<i>GSTP1</i>	rs1695	AG	Associated with better response to treatment	2A
Etoposide	Drug toxicity	Etoposide	<i>SLIT1</i>	rs2784917	CC	Associated with better response to treatment	3
			<i>ABCB1</i>	rs1045642	AG	Associated with decreased risk of drug toxicity	4
Gemcitabine	Drug toxicity	Gemcitabine	<i>RRM1</i>	rs9937	AG	Associated with decreased risk of drug toxicity	3
			<i>CDA</i>	rs60369023	AA	Associated with increased risk of drug toxicity	4
			<i>CDA</i>	rs2072671	GG	Associated with decreased risk of drug toxicity	3
Irinotecan	Drug toxicity	Irinotecan	<i>UGT1A1</i>	rs8175347	AC	Associated with increased risk of neutropenia and hematologic toxicity	2B
			<i>UGT1A1</i>	rs4148323	6TA/6TA	Associated with decreased risk of drug toxicity	2A
			<i>C8orf34</i>	rs1517114	GG	Associated with decreased risk of drug toxicity	2A
Methotrexate	Drug toxicity	Methotrexate	<i>MTHFR</i>	rs1801133	CG	Associated with increased risk of drug toxicity	2B
			<i>MTRR</i>	rs1801394	GG	Associated with decreased risk of drug toxicity	3
			<i>ABCB1</i>	rs1045642	AA	Associated with decreased risk of drug toxicity	2B
	Drug efficacy	Methotrexate	<i>ATIC</i>	rs4673993	AG	Associated with increased risk of drug toxicity	2A
Pemetrexed	Drug efficacy	Pemetrexed	<i>MTHFR</i>	rs1801133	CT	Associated with moderate response to treatment	2B
Platinum-Based Chemotherapy	Drug toxicity	Cisplatin	<i>XPC</i>	rs2228001	GG	Associated with better response to treatment	3
		Platinum compounds	<i>GSTP1</i>	rs1695	GG	Associated with increased risk of drug toxicity	1B
		Cisplatin, Platinum, Platinum compounds	<i>ERCC1</i>	rs3212986	AG	Associated with increased risk of drug toxicity	2A
		Carboplatin, Cisplatin, Oxaliplatin, Platinum, Platinum compounds	<i>ERCC1</i>	rs11615	AC	Associated with increased risk of drug toxicity	2B
	Drug efficacy	Carboplatin	<i>XRCC1</i>	rs25487	AG	Associated with increased risk of drug toxicity	2B
		Carboplatin	<i>MTHFR</i>	rs1801133	CT	Associated with decreased risk of drug toxicity	2B
		Platinum compounds	<i>XRCC1</i>	rs1799782	GG	Associated with poorer response to treatment	2A
		Carboplatin, Cisplatin, Oxaliplatin, Platinum, Platinum compounds	<i>ERCC1</i>	rs11615	GG	Associated with poorer response to treatment	NA
Taxanes	Drug toxicity	Paclitaxel	<i>ABCB1</i>	rs1045642	CT	Associated with poorer response to treatment	2B
			<i>SOD2</i>	rs4880	AG	Associated with increased risk of drug toxicity	3
		docetaxel	<i>SOD2</i>	rs4880	AG	Associated with increased risk of drug toxicity	3
			<i>ERCC1</i>	rs3212986	AG	Associated with decreased risk of drug toxicity	3

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			<i>ERCC1</i>	rs11615	AC	Associated with decreased risk of drug toxicity	3
	Taxanes		<i>ABCB1</i>	rs2032582	AG	Associated with decreased risk of drug toxicity	3
	Drug efficacy	Paclitaxel+Cisplatin	<i>TP53</i>	rs1042522	CC	Associated with decreased risk of drug toxicity	3
		Paclitaxel	<i>ABCB1</i>	rs2032582	CC	Associated with better response to treatment	2B
Vinca alkaloids	Drug efficacy	Vincristine	<i>ABCB1</i>	rs1045642	CC	Associated with poorer response to treatment	3

Note:

- 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.
- 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.
- 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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7. 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: -

8. 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
-	-	-



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9. Germline variants

Gene	Transcript	Exon	c.HGVS	p.HGVS	Zygoty	Classification
BRCA2	NM_000059.3	EX11	c.6141delT	p.Tyr2047Ter	Heterozygosity	Pathogenic

Note:

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

10. HLA-I Polymorphism variation

Somatic HLA-I Zygoty

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](https://pubmed.ncbi.nlm.nih.gov/29217585/)).

Gene	Test Content	Result
HLA-A	Zygoty	Heterozygosity
HLA-B	Zygoty	Heterozygosity
HLA-C	Zygoty	Heterozygosity



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11. Clinical Trials to consider

BRCA2 associated clinical trials

<u>NCT04601441</u>		Phase 4
Title	Study to Evaluate ctDNA of mCSPC Patients Receiving Apalutamide in Japan	
Treatment	Apalutamide	
Location	Japan	
<u>NCT04038502</u>		Phase 2
Title	Carboplatin or Olaparib for BRCA Deficient Prostate Cancer	
Treatment	Carboplatin Olaparib	
Location	United States	
<u>NCT05327010</u>		Phase 2
Title	Testing the Combination of the Anti-cancer Drugs ZEN003694 (ZEN-3694) and Talazoparib in Patients With Advanced Solid Tumors, The CombET Trial	
Treatment	BET Bromodomain Inhibitor ZEN-3694 Biopsy Biospecimen Collection Diagnostic Imaging Talazoparib	
Location	United States	
<u>NCT05498272</u>		Phase 2
Title	Study of Neoadjuvant PARP Inhibition Followed by Radical Prostatectomy in Patients With Unfavorable Intermediate-Risk or High-Risk Prostate Cancer With BRCA1/2 Gene Alterations	
Treatment	Olaparib LHRH agonist	
Location	United States	
<u>NCT03767075</u>		Phase 2
Title	A Modular Multi-Basket Trial to Improve Personalized Medicine in Cancer Patients (Basket of Baskets)	
Treatment	Atezolizumab Futibatinib Amivantamab	
Location	France, Germany, Italy, Netherlands, Spain, Sweden, United Kingdom	



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<u>NCT04030559</u>		Phase 2
Title	Niraparib Before Surgery in Treating Patients With High Risk Localized Prostate Cancer and DNA Damage Response Defects	
Treatment	Niraparib Niraparib Tosylate Monohydrate Radical Prostatectomy	
Location	United States	

<u>NCT03428802</u>		Phase 2
Title	Pembrolizumab in Treating Participants With Metastatic, Recurrent or Locally Advanced Cancer and Genomic Instability	
Treatment	Laboratory Biomarker Analysis Pembrolizumab	
Location	United States	

<u>NCT03297606</u>		Phase 2
Title	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)	
Treatment	Olaparib Dasatinib Nivolumab plus Ipilimumab Axitinib Bosutinib Crizotinib Palbociclib Sunitinib Temezirolimus Erlotinib Trastuzumab plus Pertuzumab Vemurafenib plus Cobimetinib Vismodegib Tucatinib	
Location	Canada	

<u>NCT05252390</u>		Phase 1 Phase 2
Title	NUV-868 as Monotherapy and in Combination With Olaparib or Enzalutamide in Adult Patients With Advanced Solid Tumors	
Treatment	NUV-868 Olaparib Enzalutamide	
Location	United States	

<u>NCT04991480</u>		Phase 1 Phase 2
Title	A Study of ART4215 for the Treatment of Advanced or Metastatic Solid Tumors	
Treatment	ART4215 Talazoparib Niraparib	
Location	United States, United Kingdom	

<u>NCT05417594</u>		Phase 1 Phase 2
Title	Study of AZD9574 as Monotherapy and in Combination With Anti-cancer Agents in Participants With Advanced Solid Malignancies	
Treatment	AZD9574 Temozolomide [11C]AZ1419 3391	

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Location	United States, Australia, Germany, Korea, Republic of, Spain, Sweden, United Kingdom
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<u>NCT04890613</u>	Phase 1
Title	Study of CX-5461 in Patients With Solid Tumours and BRCA1/2, PALB2 or Homologous Recombination Deficiency (HRD) Mutation
Treatment	CX-5461
Location	United States, Canada

<u>NCT05694715</u>	Phase 1
Title	Combination Therapy in Cancers With Mutations in DNA Repair Genes
Treatment	Niraparib Irinotecan
Location	United States

<u>NCT04182516</u>	Phase 1
Title	Study of NMS-03305293 in Pts With Selected Advanced/Metastatic Solid Tumors
Treatment	NMS-03305293
Location	United States, China, Italy

<u>NCT05787587</u>	Phase 1
Title	A Study of PARG Inhibitor IDE161 in Participants With Advanced Solid Tumors
Treatment	IDE-161
Location	United States

Press [here](#) for a live search of clinical trials for BRCA2



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12. Appendix

12.a. Immune checkpoint inhibitors predictive biomarkers

Tumor Mutation Burden (TMB)

bTMB (blood-based tumor mutational burden) usually refers to the number of somatic nonsynonymous mutations or all mutations per megabase in the gene region examined by whole exome sequencing or targeted sequencing in a tumor peripheral blood sample. bTMB is derived from DNA released into blood circulation by tumor cells (circulating tumor - ctDNA). Tissue TMB (tTMB) is approved as a tumor agnostic biomarker for immunotherapy in patients with metastatic solid tumors. bTMB is positively correlated with tTMB, which can reflect the level of TMB in tumor tissues to some extent. Studies have shown that bTMB is not correlated with the expression of PD-L1 in tumor tissues ([PMID: 30082870](#)).

A retrospective analysis confirmed correlation between tTMB and bTMB in patients with NSCLC included in the OAK (NCT02008227, n=850) and Poplar (NCT01903993, n=287) clinical trials of Atezolizumab in second-line treatment for advanced non-small cell lung cancer. High TMB was associated with response to immunotherapy in both trials. A different study successfully correlated blood and tissue TMB results on 2000 NSCLC samples from Geneplus database. The correlation of bTMB with outcomes after front line treatment with Pembrolizumab and Pembrolizumab plus Chemotherapy was also evaluated, at a cutoff of ≥ 16 mut/Mb, in 66 pts with mNSCLC. Early results suggested that bTMB may predict therapeutic outcomes after first line Pembrolizumab based therapy in mNSCLC. However, the prospective phase III BFAST trial concluded that bTMB at a cut-off of ≥ 16 mut/Mb was not a predictive biomarker for clinical outcomes with atezolizumab in patients with previously untreated metastatic NSCLC, although the 18-month PFS and OS both numerically favored atezolizumab in this bTMB group ([PMID: 35995953](#)).

Evaluation of tissue- and plasma-derived TMB from the CheckMate 848 clinical trial, showed that at the prespecified cutoff of 10 mut/Mb, 15.8% and 20.7% of samples had high tTMB and bTMB, respectively; the positive (PPA), negative and overall percentage agreements between assays were 60%, 88%, and 84%, respectively. TMB correlation (Spearman's r , 0.54; $P < 0.0001$) and PPA (66%) were improved among 806 (79.3%) sample pairs with plasma maximum somatic allele frequency $\geq 1\%$ (<https://doi.org/10.1158/1538-7445.AM2022-2139>).

Plasma samples with high bTMB values are highly correspondent with tTMB, whereas bTMB low results may also be the result of low tumor burden at earlier stages of disease as well as poorly shedding tumors (PMID: 35217576). Typically, bTMB reports higher than tTMB, as reported in Drusbosky et al, who analyzed 5610 blood specimens with the 80th percentile bTMB being ≥ 16 mut/Mb tissue equivalency ([PMID: 35274716](#)).

At present, there is no consensus on the application of bTMB in clinical cancer treatment.

Table S1. TMB interpretation and cut-offs.

Tumour Type	Immunotherapy agent	Study/Trial	TMB high cut-off	Type of benefit
NSCLC	Anti PD-L1	B1FIRST [1]	≥ 16 Muts/Mb	ORR
NSCLC	Anti PD-L1	BFAST Cohort C [2]	≥ 16 Muts/Mb	-
NSCLC	Anti PD-L1	MYSTIC [3]	≥ 20 Muts/Mb	OS
NSCLC	Anti PD-L1	OAK [4]	≥ 16 Muts/Mb	PFS
NSCLC	Anti PD-L1	POPLAR [4]	≥ 16 Muts/Mb	PFS

1. Mok, Tony & Gadgeel, S. & Kim, et al. Blood first line ready screening trial (B-F1RST) and blood first assay screening trial (BFAST) enable clinical development of novel blood-based biomarker assays for tumor mutational burden (TMB) and somatic mutations in 1L advanced or metastatic NSCLC. 2017. Annals of Oncology. 28. 10.1093/annonc/mdx380.084. | 2. Peters S, et al. Atezolizumab versus chemotherapy in advanced or metastatic NSCLC with high blood-based tumor mutational



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burden: primary analysis of BFAST cohort C randomized phase 3 trial. Nat Med. 2022 Sep;28(9):1831-1839. | 3. Rizvi NA, et al. MYSTIC Investigators. Durvalumab With or Without Tremelimumab vs Standard Chemotherapy in First-line Treatment of Metastatic Non-Small Cell Lung Cancer: The MYSTIC Phase 3 Randomized Clinical Trial. JAMA Oncol. 2020 May 1;6(5):661-674. doi: 10.1001/jamaoncol.2020.0237. | 4. Gandara DR, et al. Blood-based tumor mutational burden as a predictor of clinical benefit in non-small-cell lung cancer patients treated with atezolizumab. Nat Med. 2018 Sep;24(9):1441-1448. doi: 10.1038/s41591-018-0134-3.

Microsatellite Instability (MSI)

MSI (microsatellite instability, MSI) refers to the phenomenon that the sequence of microsatellites increases or decreases. Microsatellite (MS), also called Short Tandem Repeats (STRs) or Simple Sequence Repeat (SSRs), consists of repeated sequences of 1-6 nucleotides. This report uses NGS panel detection and is based on the 1021 Panel platform. 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).

FDA approved pembrolizumab for solid tumors with MSI-H or dMMR (highly unstable microsatellites or MMR defects) and approved for MSI-H or dMMR colorectal cancer as the first-line treatment ([PMID: 35680043](#), [33264544](#)). FDA approved nivolumab for the treatment of children or adults who have progressed after 5-FU/oxaliplatin/irinotecan treatment with MSI-H or dMMR metastatic colorectal cancer. The NCCN clinical practice guidelines for colorectal cancer indicate that pembrolizumab/nivolumab can be used for the treatment of patients with dMMR/MSI-H colorectal cancer ([PMID: 28734759](#)).



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12.b. Methodology

ctDNA analysis was performed using plasma-extracted cfDNA, in combination with DNA extracted from leukocytes as a control to avoid the detection of false positive results due to clonal hematopoiesis mutations. The MagMAX Cell-Free DNA Isolation Kit (ThermoFischer Scientific) and the MagCore Genomic DNA Whole Blood Kit (RBC Bioscience) were used for cfDNA and genomic DNA extraction respectively. A capture based targeted next generation sequencing (NGS) analysis was performed, using the Oncology Multi-Gene Variant Assay (GenePlus) which is a qualitative 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-G400). 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.

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 30 ng of gDNA input for library preparation.

Variant Type	Limit of Detection
Single nucleotide variations (SNV)	VAF \geq 0.5%
Insertions/deletions (Indel)	VAF \geq 0.5%
Fusion (or rearrangement)	VAF \geq 0.5%

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 follows 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).

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Limitations

1. The test is limited to test genomic variations on DNA level and does not involve RNA level or protein level.
2. Limited cell free tumor DNA (ctDNA) amount could result in false negative results.
3. Scientific data show that not all patients carry genomic variations that are associated with targeted drug, therefore not all subjects can be matched with targeted therapies or clear resistance mechanism.
4. Genetic variation beyond the detection range of this test or some non-gene mutation related factors such as drug interactions may affect the clinical effects of drugs.
6. 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%.
7. 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.



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12.d. Quality Control Results

Quality Control Index	Result	Criterion	
Sequencing Quality Assessment	Average effective sequencing depth ¹	3373	≥ 1000
	Fraction of target covered with ≥ 50x ²	100%	≥99%
	Fraction of base quality ≥ Q30 ³	96.30%	≥80%
Overall Assessment ⁴	PASS		

Note :

1. Average effective sequencing depth: Average sequencing depth on target without duplicated reads.
2. Fraction of target covered with ≥ 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. Overall Assessment: The quality control overall assessment results are divided into two levels: "PASS" and "RISK". TWhen 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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12.e. 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	ERRF1	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	PKD1	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	ADAMTSS	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
SUCLG1	SUCLG2	SULT1A1	SUZ12	SVEP1	SYNCRIP	SYNE1	TAF1	TAF15	TAF1L
TAL1	TBL1XR1	TBX15	TBX22	TCEB1	TCF12	TCF3	TCF4	TCL1A	TEC

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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	

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12.f. Levels of Evidence for Genomic Biomarkers

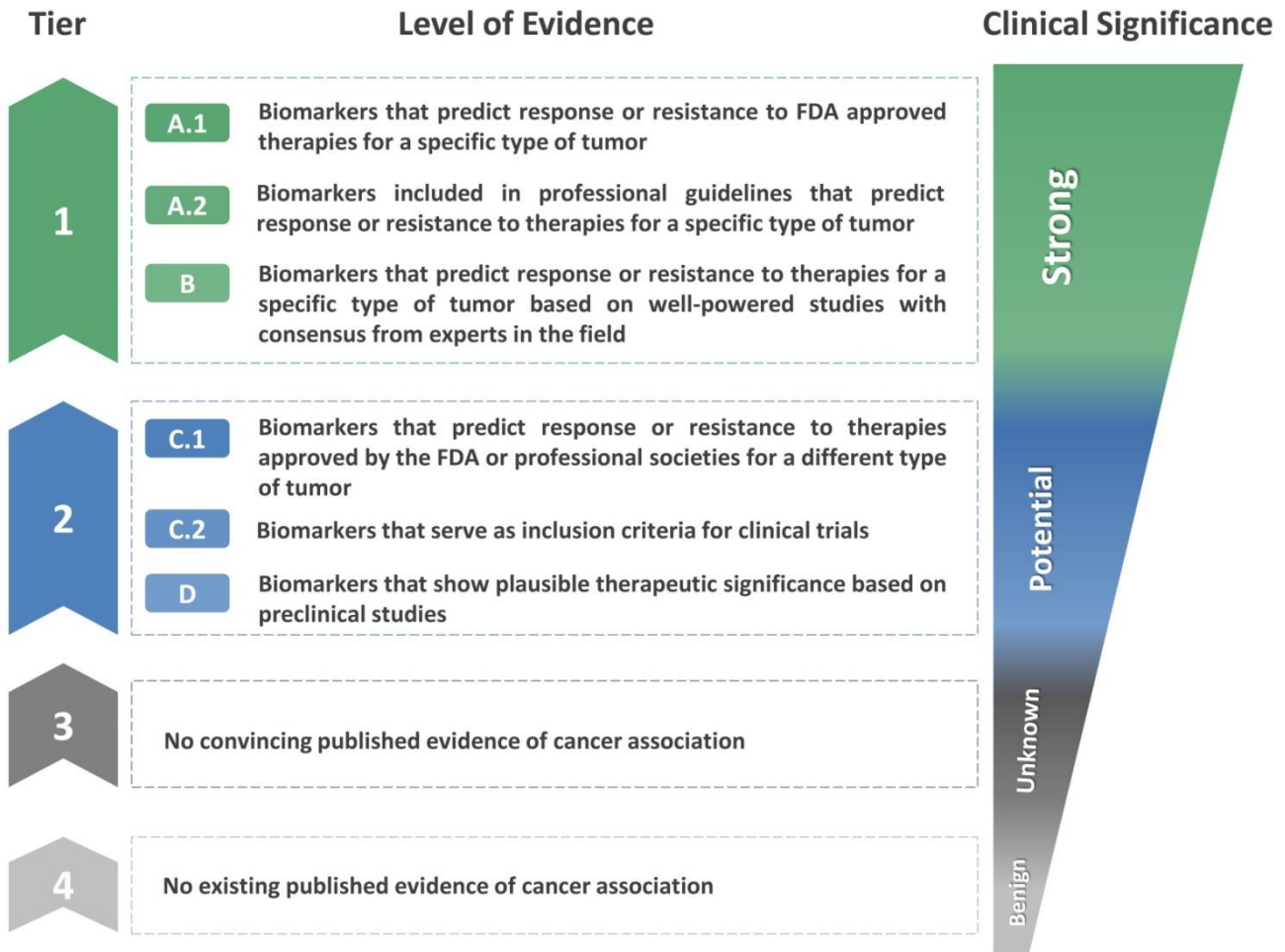


Figure 1. Joint consensus recommendation of AMP, ACMG, ASCO and CAP for reporting genetic variants in cancer. [1-2]

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18. <https://pmkb.org/>



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