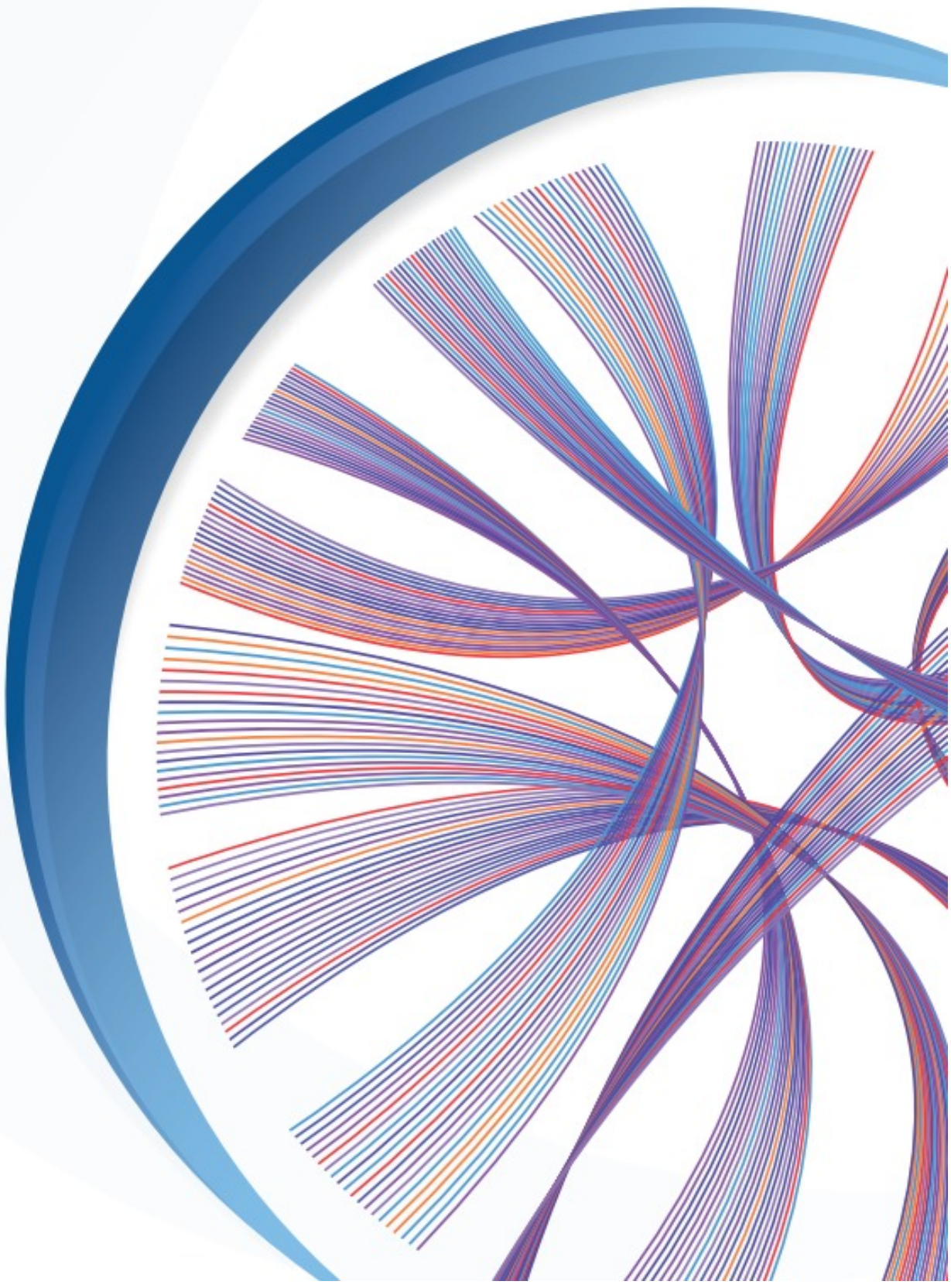
4baseCare
Together, We Beat Cancer

TARGT First

TEST REPORT



PATIENT ID	CANCER SITE	SAMPLE ID	REGISTRATION DATE
IN-423-WCBC	OVARY	IN-423-WCBC-F	02/03/2023

SCOPE OF THE TEST

SNVs, InDels, CNAs, Gene Fusions status

CLINICAL INDICATION

Ovarian Carcinoma

REPORT DETAILS

Name : SUNITA

Gender : Female

Age/DOB : 40 Years

Reporting Date : 17/03/2023

Cancer Celltype : Carcinoma, NOS

Sample Source : AH-91/23 A,B

Tumor content : 50%

Consulting Clinician : Dr. Amit Jain

Hospital : Valentis Cancer Hospital, Mussoorie Mawana Road

RESULTS

GENOMIC FINDINGS FROM TUMOR PROFILING

Genomic Alteration

BRCA1 Exon 10 (p.Trp372GlyfsTer2)

Allelic burden: 64%

Relevant Therapies (in Same Cancer Type)

Therapy	*Clinical Relevance*
Olaparib	RESPONSIVE
Rucaparib	RESPONSIVE
Niraparib	RESPONSIVE
Olaparib, Bevacizumab	RESPONSIVE

Relevant Therapies (in Different Cancer)

Therapy	*Clinical Relevance*	*Cancer Type*
Olaparib	RESPONSIVE	Breast cancer
Talazoparib	RESPONSIVE	Breast cancer
Rucaparib	RESPONSIVE	Prostate cancer
Olaparib	RESPONSIVE	Prostate cancer

**NA: Not Applicable*

STATUS OF VARIANTS IN CANCER RELATED BIOMARKERS

Gene	*BRCA1*	*ATM*	*BARD1*	*BRIP1*	*CDK12*	*CHEK1*	*CHEK2*	*FANCL*
Status	Pathogenic	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected

Gene	*PALB2*	*PPP2R2A*	*RAD51B*	*RAD51C*	*RAD51D*	*RAD54L*	*PIK3CA*	*KRAS*	*BRCA2*
Status	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected

Note:

While we have detected a pathogenic mutation in the *BRCA1* (chr17:g.41246435delA; c.1114del; p.Trp372GlyfsTer2) gene in the tumor sample of this patient, the possibility of a germline mutation cannot be ruled out. We suggest reflex germline testing for the same.

4baseCare Oncosolutions Pvt. Ltd

Vaishnavi Signature No. 78/9, Outer Ring Road,

Bellandur Village Varthur Hobli

Bengaluru-560103, Karnataka, India

**Please note that this is not a medical report*

PATIENT ID	CANCER SITE	SAMPLE ID	REGISTRATION DATE
IN-423-WCBC	OVARY	IN-423-WCBC-F	02/03/2023

VARIANT DETAILS:

Gene	Variant Location	Variant Consequence	Clinical Significance	Variant Type	Reference
BRCA1	chr17:g.41246435delA, ENST00000471181, Exon 10	c.1114del, p.Trp372GlyfsTer2 , 64%	Pathogenic	Frameshift Deletion	ACMG Guidelines
MSH6	chr2:g.48027417C>G, ENST00000234420, Exon 4	c.2295C>G,p.Cys765Trp , 42%	VUS	Nonsynonymous SNV	rs63750985, VCV000089265.10

**NA: Not Applicable*

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VARIANTS WITH CLINICALLY RELEVANT THERAPIES

Gene (Variant) - Drug association	Summary
• *BRCA1*: Olaparib - RESPONSIVE	The drug olaparib has been approved for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated (gBRCAm or sBRCAm) advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy (FDA). The approval was based on the SOLO-1 (NCT01844986) trial, a randomized (2:1), double-blind, placebo-controlled, multi-center trial that compared the efficacy of olaparib (n=260) with placebo(n=131). Estimated median PFS was not reached in the olaparib arm and was 13.8 months in the placebo arm (HR 0.30; 95% CI: 0.23-0.41; p<0.0001). The trial demonstrated a statistically significant improvement in PFS for olaparib with a 70% lower risk of disease progression compared to placebo.
• *BRCA1*: Rucaparib - RESPONSIVE	The drug rucaparib has been approved for the maintenance treatment of BRCA mutated recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy (FDA). The approval was based on the clinical study ARIEL3 (NCT01968213). 372/561 patients were treated with rucaparib. The median progression free survival for the rucaparib treatment arm was 10.8 months; HR 0.36; 95% CI:0.30, 0.45; >0.0001) and 5.4 months in the Placebo arm. Rucaparib significantly improved PFS vs placebo in all primary analysis groups of patients with platinum-sensitive recurrent ovarian carcinoma.
• *BRCA1*: Niraparib - RESPONSIVE	The drug niraparib has been approved 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 (FDA). The approval was based on PRIMA (NCT02655016). 373 of 733 patients who were newly diagnosed with advanced ovarian cancer included in the study had homologous recombination deficiency (HRD) status (tumor BRCA mutation/genomic instability score≥42). Median progression free survival was 21.9 months (HR 0.43; 95% CI: 0.31, 0.59; p<0.0001) among the HRD status positive patients and 13.8 months (HR 0.62; 95% CI: 0.50, 0.76; p<0.0001) for the overall population who received niraparib.
• *BRCA1*: Olaparib, Bevacizumab - RESPONSIVE	The drug olaparib in combination with bevacizumab has been approved for first-line 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 (FDA). The approval was based on the PAOLA-1 (NCT03737643) trial, the drug olaparib was randomised (2:1) twice daily in combination with bevacizumab (n=537) or placebo plus bevacizumab (n=269). In the subgroup of 387 patients with HRD-positive tumours, the median PFS was 37.2 months in the olaparib plus bevacizumab arm and 17.7 months in the placebo plus bevacizumab arm (HR 0.33; 95 percent CI: 0.25-0.45).
• *BRCA1*: Olaparib - RESPONSIVE Breast cancer	The drug Olaparib has been approved for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), HER2-negative metastatic breast cancer (FDA). The approval was based on the clinical study OlympiAD (NCT0200062), A total of 205 patients were randomized to olaparib and 97 to TPC (capecitabine, vinorelbine, or eribulin). The median OS was 19.3 months with olaparib versus 17.1 months with TPC (HR 0.90, 95% CI 0.66-1.23; P = 0.513); median follow-up was 25.3 and 26.3 months, respectively.

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VARIANTS WITH CLINICALLY RELEVANT THERAPIES

Gene (Variant) - Drug association	Summary
• *BRCA1*: Talazoparib - RESPONSIVE Breast cancer	The drug talazoparib has been approved for patients who have deleterious or suspected deleterious germline BRCA-mutated (g*BRCA*m), HER2-negative locally advanced or metastatic breast cancer (FDA). The approval was based on the EMBRACA clinical study (NCT01945775). Talazoparib was given to 287 out of 431 patients. The median progression-free survival in the talazoparib and chemotherapy arms was 8.6 and 5.6 months, respectively (HR 0.54; 95%CI: 0.41, 0.71; p0.0001). Talazoparib as a single agent provided a significant benefit over standard chemotherapy.
• *BRCA1*: Rucaparib - RESPONSIVE Prostate cancer	The drug Rucaparib has been approved for patients with androgen receptor-directed therapy and taxane-based chemotherapy who have a deleterious BRCA mutation (germline and/or somatic) and metastatic castration-resistant prostate cancer (mCRPC) (FDA). The approval was based on the TRITON2 clinical study (NCT02952534). Rucaparib was administered to 115 patients. In 62 patients with measurable disease, the objective response rate (ORR) and duration of response (DOR) were measured. The confirmed ORR was 44%. (95 percent CI: 31, 57). The median duration of response could not be calculated (NE; 95 percent CI: 6.4, NE). The DOR ranged from 1.7 to 24 months. 15 of the 27 patients (56%) with confirmed objective responses had a DOR of 6 months. Rucaparib demonstrated good efficacy in patients with mCRPC and a germline or somatic BRCA/DDR gene mutation.
• *BRCA1*: Olaparib - RESPONSIVE Prostate cancer	The drug olaparib has been approved 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 (FDA). The approval was based on PRO found (NCT02987543). The study included patients harboring *BRCA1, BRCA2* and *ATM* mutations (cohort A) and patients harboring mutations in 12 genes related to HRR pathway (cohort B). A median 7.4 months progression free survival was recorded based on imaging (HR 0.34; 95% CI, 0.25, 0.47; p<0.001) with median overall survival of 18.5 months in cohort A. Confirmed objective response of 33% among 28/84 patients evaluable in the olaparib group in cohort A.

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TEST DESCRIPTION

TAR**GT** First is a Next Generation Sequencing based test which identifies genetic alterations in a comprehensive panel of well curated 53 tumor genes which can impact response to approved therapy for a particular cancer type. Some of the alterations detected may have bearing on prognosis and/or therapeutic options and may provide relevant information that allows oncologists/clinicians to consider various lines of targeted treatment for the patient.

GENES EVALUATED

TAR**GT** First detects mutations (SNVs and Short Indels), Copy Number Variations (CNVs), gene fusions and splice variants in the 53 genes :

SNVs/InDels Covered in TAR**GT** First

ABL1	*ALK*	*AR*	*ATM*	*BARD1*	*BRAF*	*BRCA1*	*BRCA2*	*BRIP1*	*CDK12*
CDK4	*CDK6*	*CDKN2A*	*CHEK1*	*CHEK2*	*EGFR*	*EPCAM*	*ERBB2*	*ERBB3*	*EZH2*
FANCL	*FGFR3*	*GAPDH*	*IDH1*	*IDH2*	*JAK2*	*KIT*	*KRAS*	*MAP2K1*	*MAP2K2*
MDM2	*MET*	*MLH1*	*MLH3*	*MSH2*	*MSH6*	*NRAS*	*PALB2*	*PDGFRA*	*PDGFRB*
PIK3CA	*PMS1*	*PMS2*	*PPP2R2A*	*RAD51B*	*RAD51C*	*RAD51D*	*RAD54L*	*RET*	*ROS1*
STK11	*TSC1*	*TSC2*							

CNAs Covered in TAR**GT** First

ABL1	*AR*	*ATM*	*BARD1*	*BRCA1*	*BRCA2*	*BRIP1*	*CDK12*	*CDK4*	*CDK6*
CDKN2A	*CHEK1*	*CHEK2*	*EGFR*	*EPCAM*	*ERBB2*	*ERBB3*	*EZH2*	*FANCL*	*FGFR3*
GAPDH	*IDH2*	*JAK2*	*KIT*	*MDM2*	*NRAS*	*PALB2*	*PDGFRA*	*PDGFRB*	*PPP2R2A*
RAD51B	*RAD51C*	*RAD51D*	*RAD54L*	*STK11*	*TSC1*	*TSC2*			

Gene Fusions Covered in TAR**GT** First

ALK	*MET*	*RET*	*ROS1*

TEST METHODOLOGY

Sample preparation and Library preparation :

DNA isolated from FFPE, or any other fresh tumor tissue source was used to perform targeted gene capture using a custom capture kit. The libraries were sequenced to mean >250X coverage on Illumina sequencing platform.

Bioinformatics Analysis and Reporting :

The sequences obtained are aligned to human reference genome (GRCh37/hg19) and variant analysis was performed using set of Bioinformatics Pipeline. Only non-synonymous and splice site variants found in the panel consisting of specific set of genes were used for clinical interpretation. Silent variations that do not result in any change in amino acid in the coding region are not reported. Clinically relevant mutations were annotated using published variants in literature and a set of databases – ClinVar, COSMIC and dbSNP. Common variants are filtered based on allele frequency in 1000 Genome Phase 3, ExAC, dbSNP, gnomAD, etc. In the absence of a clinically significant reported known variation(s), pathogenicity will be predicted based on in-silico gene prioritization tools: CADD, SIFT, PolyPhen-2, Condel and Mutation taster and prioritized for clinical correlation. The identified pathogenic variant will be correlated with observed phenotypic features of the patient and interpreted according to American College of Medical Genetics (ACMG) guidelines.
Somatic variants are classified into two tiers based on their level of clinical significance in cancer diagnosis, prognosis, and/or therapeutics as per international guidelines: ACMG, ASCO, AMP, CAP, NCCN and ESMO

LIMITATIONS AND DISCLAIMER

- DNA studies do not constitute a definitive test for the selected condition(s) in all individuals. It should be realized that there are possible sources of error. Errors can result from trace contamination, rare technical errors, rare genetic variants that interfere with analysis, recent scientific developments, and alternative classification systems. This test should be one of the many aspects used by the healthcare provider to help with a diagnosis and treatment plan.
- We are using the canonical transcript for clinical reporting which is usually the longest coding transcript with strong/multiple supporting evidence. However, in rare cases, clinically relevant variants annotated in alternate complete coding transcripts could also be reported.
- The contents of this test should be carefully assessed by the treating physician and further interpreted along with clinical, histopathological findings, contraindications and guidelines before deciding the course of therapy.
- The chromosomal aberrations like copy number variations and rearrangements may not be reliably detected with this assay and have to be confirmed by alternate method.
- The sensitivity of this assay to detect large deletions/duplications of more than 10 bp or copy number variations (CNV) is 70-75%. The CNVs detected have to be confirmed by alternate method.
- Most recent block is recommended for testing as the mutation profile may change in response to treatment and hence differ at different sampling points.
- TARGT FIRST test has been developed, validated and performed by 4baseCare Genomics Pvt. Ltd and has not been cleared or approved by the FDA.
- The identified pathogenic variant will be correlated with observed phenotypic features of the patient and interpreted according to (ASCO) guidelines.
- Certain genes may not be covered completely, and few mutations could be missed. A negative result cannot rule out the possibility that the tested tumor sample carries mutations not previously associated with cancer and hence not included in the panel.