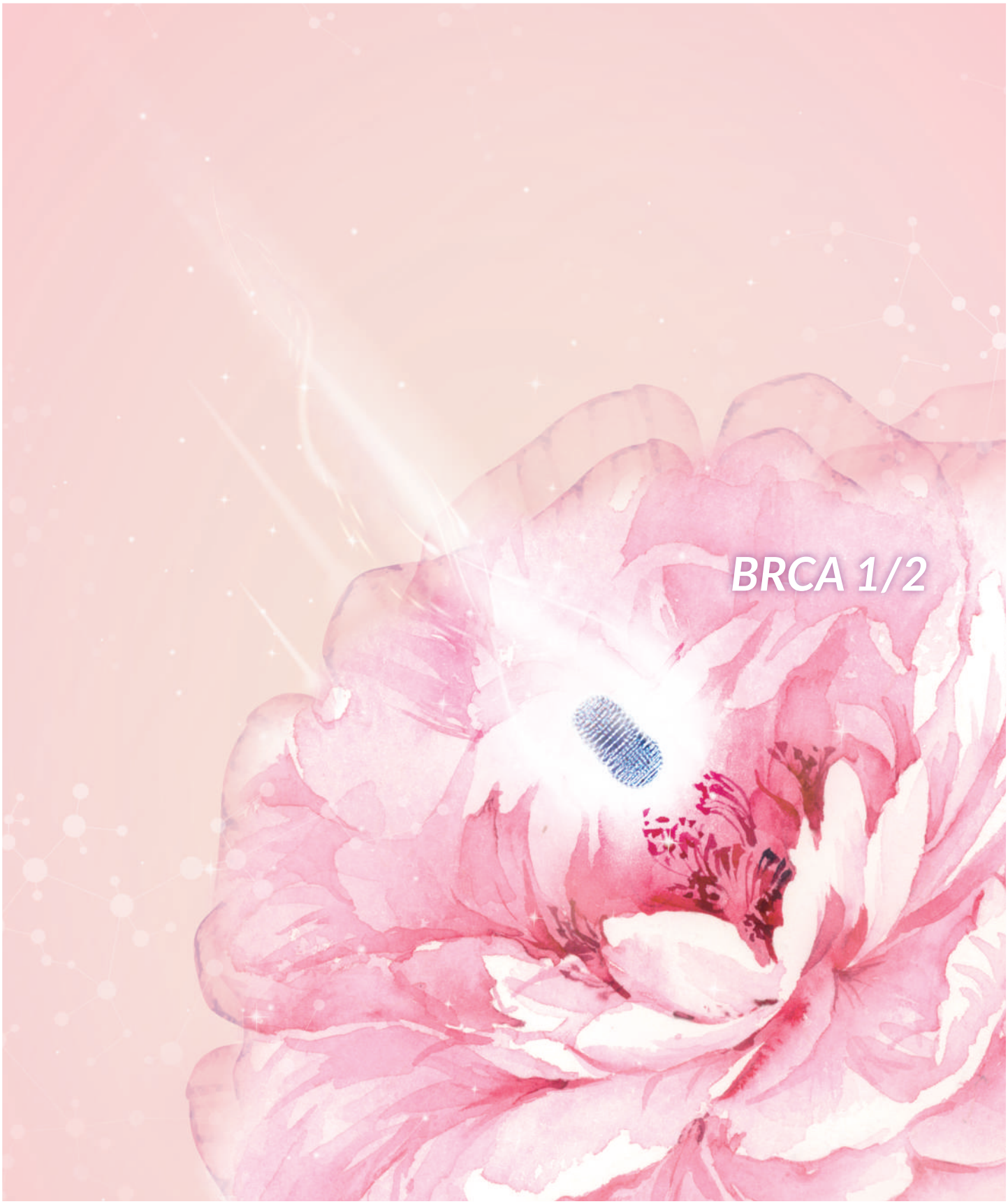


ACT BRCA®

PRECISELY IDENTIFY BRCA MUTATION

ACT GENOMICS®

ACT BRCA® Technical Specifications

	ACT BRCA® Blood	ACT BRCA® Tissue
Specimen Requirements	4-8 ml blood	Tumor Tissue (FFPE) 5-20 unstained sections (5 μm/slide, surface area ≥ 125 mm^2) 1 H&E stained slide (5μm)
LGR	*BRCA1 & BRCA2*	
Types of Mutations Genes Analyzed[1,2]	SNV , Small InDel , LGR	
Sequencing Mean Depth	≥1000X	
Sensitivity[3]	100% [95% CI: 93.40%, 100.00%]	100% [95% CI: 84.54%, 100.00%]
Specificity[3]	100% [95% CI: 99.93%, 100.00%]	100% [95% CI: 99.97%, 100.00%]
Accuracy[3]	100% [95% CI: 99.93%, 100.00%]	100% [95% CI: 99.97%, 100.00%]
Precision[3]	100% [95% CI: 93.40%, 100.00%]	100% [95% CI: 84.54%, 100.00%]
Turnaround Time	10 Working Days (* starting from the date of receipt of qualified samples at our CAP-accredited laboratory)	

Note1. The test may return with no LGR results when insufficient tumor purity after bioinformatics analysis. Tumor purity for LGR results should be more than 30%.
Note2. It is possible that the test may return with no abnormal mutation identified for certain genes or part of the test results may not be available due to the technical limitations of the test itself and/or an individual's genetic differences. Nevertheless, please rest assured that our laboratory diligently carries out every test following a stringent procedure to ensure quality.
Note3. Data from ACT Genomics.

Hallmarks of ACT BRCA®

Complete *BRCA* Genetic Information

A comprehensive *BRCA1/2* testing which includes coding exons and splicing regions. NGS technology is used to detect multiple mutation types such as SNVs, small InDels, as well as LGRs through a proprietary algorithm (patent application in progress).

Bioinformatic Analysis based on International Databases

Up-to-date information extracted from international databases such as gnomAD, 1000 Genome, ClinVar, COSMIC, as well as ACT Genomics' self-built ethnographic database, provide relevant interpretation and useful insights on the variants identified.

A Clear and Detailed Medical Report

The report provides recommendations in accordance with the latest ACMG Guidelines and AMP Guidelines, as well as other relevant information based on the currently available clinical literature.

Quality Guaranteed

All tests carried out by ACT Genomics are conducted in a CAP-certified laboratory, which has also garnered the LDTS (Laboratory Developed Tests and Services) certification by the Taiwan FDA.

Confirmatory Test Services in Other Family Members

If a deleterious or suspected deleterious germline *BRCA1/2* variant is found in an individual, our services also include confirmatory tests which can be extended to other family members.

Note : Genetic counseling is required prior to any follow-up confirmatory testing in other family members. Additional fees and charges may apply.

ACTBRCA® Provides *BRCA1/2* Genetic Information for PARP Inhibitor Treatment Selection

BRCA1/2 is the most common gene mutation in hereditary breast cancer and has also been found to be associated with ovarian cancer, pancreatic cancer, prostate cancer, etc. In recent years, selection of cancer patients who would likely benefit from PARP inhibitor treatment also relies on the detection of *BRCA1/2* mutations, thus emphasizing the importance of *BRCA1/2* genetic testing.

BRCA1/2 Genetic Information

Individuals with deleterious or likely deleterious germline *BRCA1/2* mutations are known to have an increased lifetime risk of breast, ovarian, pancreatic, and prostate cancers[1]. Therefore, a genetic testing for germline *BRCA1/2* mutations allows the lifetime risk of hereditary cancers to be determined, so that risk mitigation actions such as active surveillance and other preventive measures can be taken timely through appropriate genetic counseling.

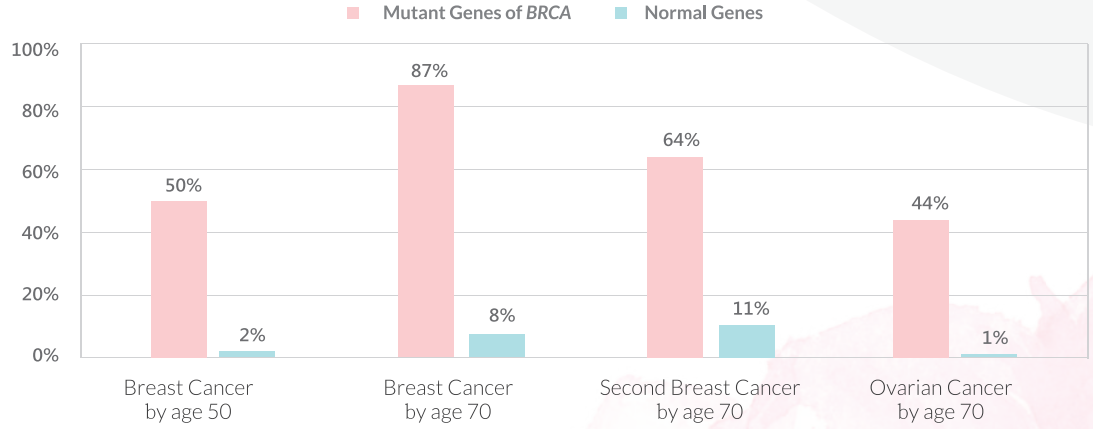


Figure1：*BRCA1/2* Gene Mutations Increase the Lifetime Risk of Breast Cancer[2,3]

According to the latest NCCN guideline[11], genetic counseling is recommended in breast cancer patients and their families if they fulfill the following characteristics:

- With a known pathogenic/likely pathogenic variant in a cancer susceptibility gene.
- Personal or family history of ovarian cancer.
- Personal or family history of bilateral breast cancer.
- Early-onset breast cancer at ≤45 years of age.
- Triple negative breast cancer at ≤60 years of age.
- At least 1 close blood relative with breast cancer at ≤50 years of age .
- At least 3 total diagnoses of breast cancer in a family.
- Family history of pancreas.
- Family history of male breast cancer.

Consultation with a physician or a professional genetic counselor is highly recommended before, during, and/or after the test

PARP Inhibitor Treatment

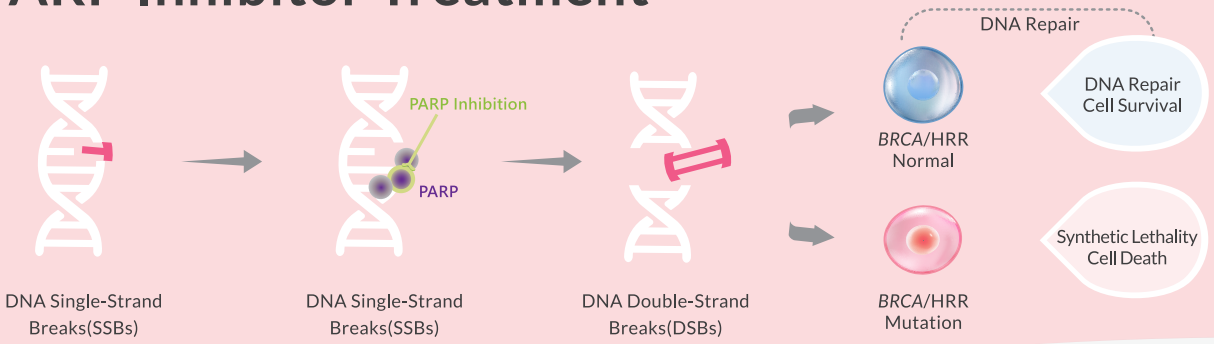
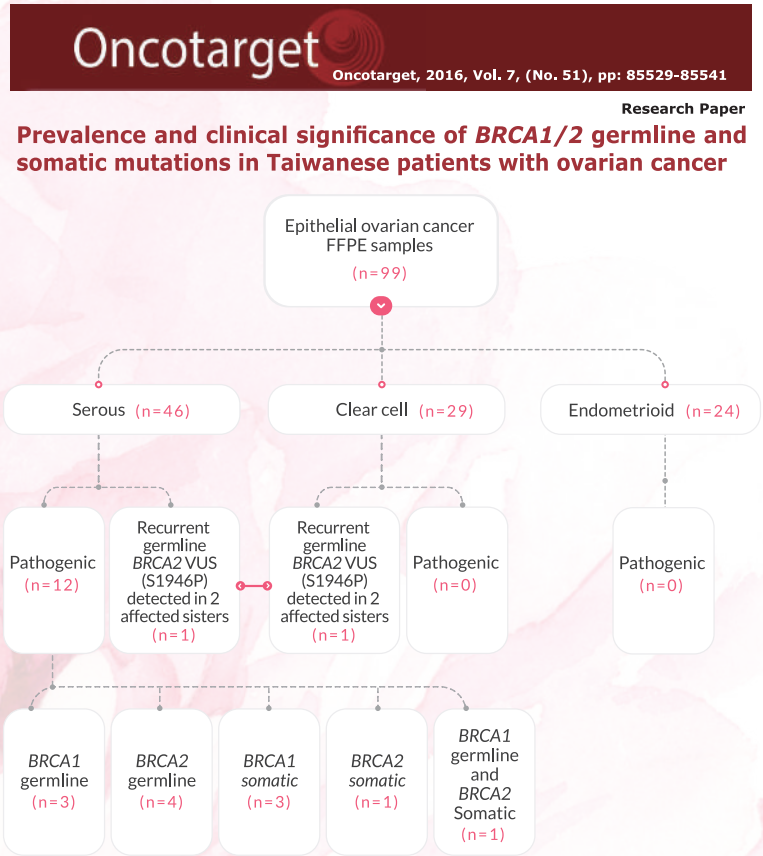


Figure2：Mechanism of Synthetic Lethality in *BRCA*/HRR Deficient Cancer[7,8,9,10]

PARP inhibitors are pharmacological agents that block the activity of a family of DNA damage repair (DDR) proteins called PARPs, which are responsible for repairing single-strand breaks before DNA replication and cell division. If the single-strand breaks remain unrepaired and persist through the DNA replication process, double-strand breaks are formed as a result. PARP inhibitors cause the formation of double-strand breaks by trapping at the sites of single-strand DNA breaks[1,4,5].

In tumors with homologous recombination repair (HRR) deficiency (also known as HRD, which is caused by mutations in *BRCA1/2* or other HRR genes), these double-strand breaks cannot be properly repaired, ultimately leading to cell death in a phenomenon called synthetic lethality whereby the combination of two individually non-lethal defects (i.e., PARP inhibition and HRD) leads to a unique vulnerability[6].

Real-Wold Experience :
Both Germline and Somatic *BRCA1/2* Mutations Play an Important Role in Cancer



1.Venkitaraman AR. Annu Rev Pathol 2009; 4: 461-487.
2.Ford D, et al. Lancet. 1994;343:692-695.
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8.Livraghi L, Garber JE. BMC Med 2015; 13:188.
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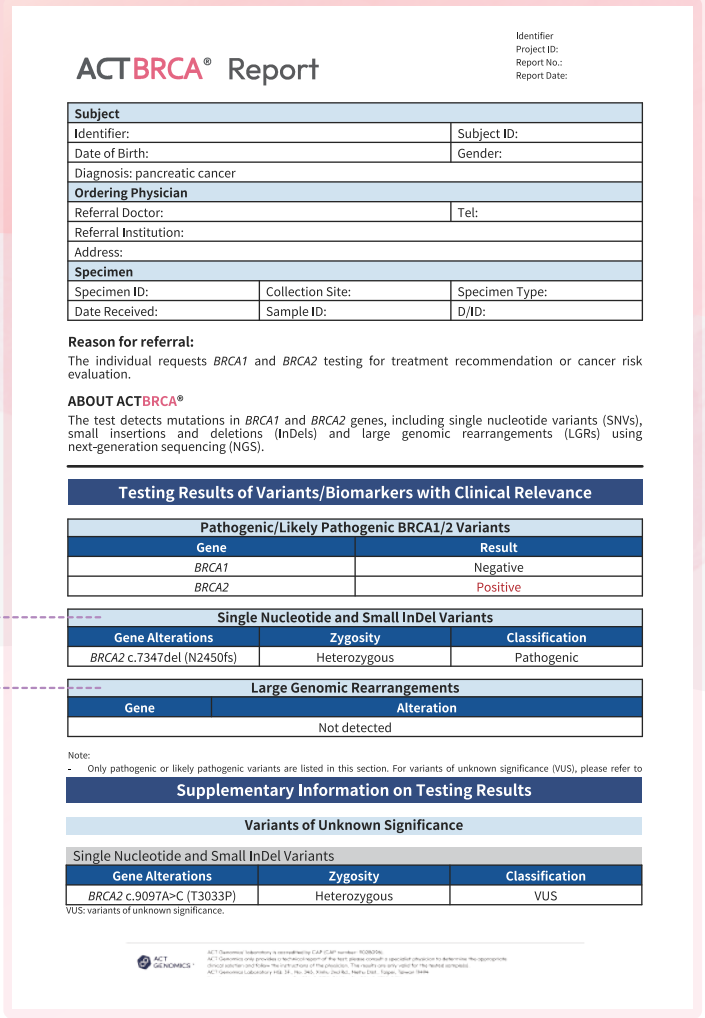
10.Bryant HE, Schultz N, Thomas HD, et al. Nature 2005; 434: 913-917
11. NCCN Guidelines Version 2.2022.

The normal and tumor tissue samples of 99 patients with ovarian cancer were analyzed for *BRCA1/2* mutations using next-generation genetic sequencing and Sanger gene sequencing. Pathogenic *BRCA1/2* variants were found in 12 patients. It is notable in one patient that both germline *BRCA1* and somatic *BRCA2* mutations were found. Interestingly, all of the 12 patients with pathogenic *BRCA1/2* mutations had serous carcinoma, suggesting that ovarian cancer with these *BRCA* gene mutations exhibit similar pathological morphology. Four of these 12 patients (~33%) had a *BRCA* gene mutation that was solely detectable in tumor tissue and not in normal tissue, indicative of the sporadic nature of these mutations. This study exemplifies that *BRCA* gene mutations, whether inherited or acquired, can play a key role in the pathogenesis of ovarian cancer.

*Abbreviations: *gBRCA*: germline *BRCA*; *sBRCA*: somatic *BRCA*.

ACTBRCA® Report



ACTBRCA® Report

Identifier
Project ID:
Report No.:
Report Date:

Subject		
Identifier:		Subject ID:
Date of Birth:		Gender:
Diagnosis: pancreatic cancer		
Ordering Physician		
Referral Doctor:		Tel:
Referral Institution:		
Address:		
Specimen		
Specimen ID:	Collection Site:	Specimen Type:
Date Received:	Sample ID:	D/ID:

Reason for referral:

The individual requests *BRCA1* and *BRCA2* testing for treatment recommendation or cancer risk evaluation.

ABOUT ACTBRCA®

The test detects mutations in *BRCA1* and *BRCA2* genes, including single nucleotide variants (SNVs), small insertions and deletions (InDels) and large genomic rearrangements (LGRs) using next-generation sequencing (NGS).

Testing Results of Variants/Biomarkers with Clinical Relevance

Pathogenic/Likely Pathogenic BRCA1/2 Variants	
Gene	**Result**
BRCA1	Negative
BRCA2	Positive

Single Nucleotide and Small InDel Variants		
Gene Alterations	**Zygosity**	**Classification**
BRCA2 c.7347del (N2450fs)	Heterozygous	Pathogenic

Large Genomic Rearrangements	
Gene	**Alteration**
Not detected	

Note:
- Only pathogenic or likely pathogenic variants are listed in this section. For variants of unknown significance (VUS), please refer to

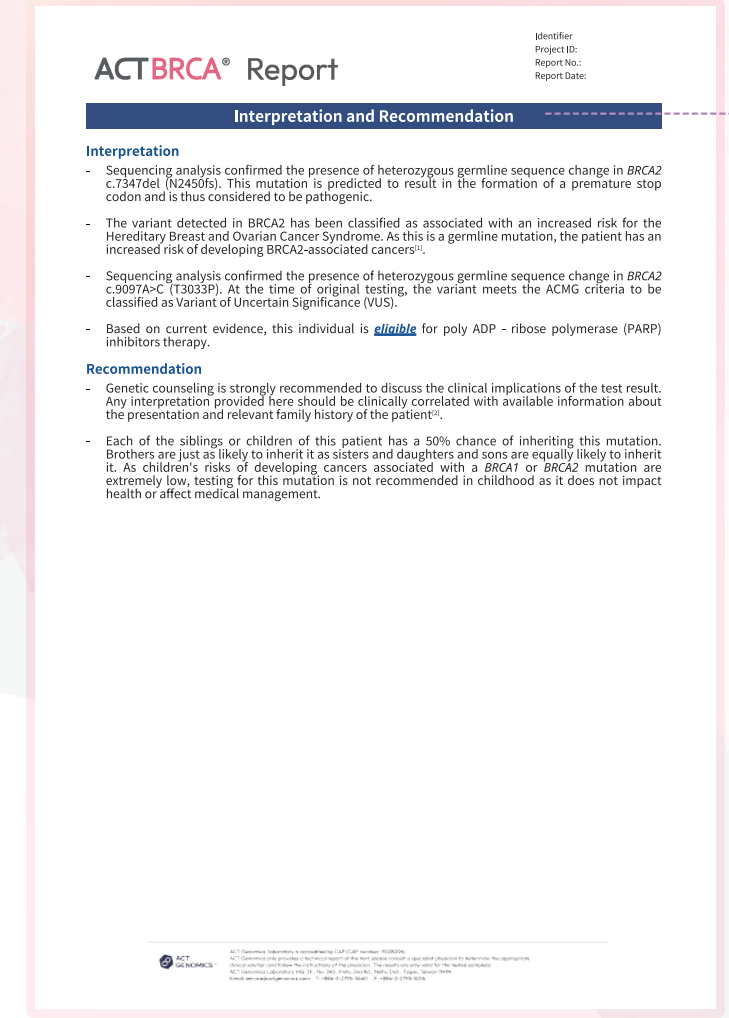
Supplementary Information on Testing Results

Variants of Unknown Significance

Single Nucleotide and Small InDel Variants

Gene Alterations	Zygosity	Classification
BRCA2 c.9097A>C (T3033P)	Heterozygous	VUS

VUS: variants of unknown significance.



ACTBRCA® Report

Identifier
Project ID:
Report No.:
Report Date:

Interpretation and Recommendation

Interpretation

- Sequencing analysis confirmed the presence of heterozygous germline sequence change in *BRCA2* c.7347del (N2450fs). This mutation is predicted to result in the formation of a premature stop codon and is thus considered to be pathogenic.
- The variant detected in BRCA2 has been classified as associated with an increased risk for the Hereditary Breast and Ovarian Cancer Syndrome. As this is a germline mutation, the patient has an increased risk of developing BRCA2-associated cancers[1].
- Sequencing analysis confirmed the presence of heterozygous germline sequence change in *BRCA2* c.9097A>C (T3033P). At the time of original testing, the variant meets the ACMG criteria to be classified as Variant of Uncertain Significance (VUS).
- Based on current evidence, this individual is ***eligible*** for poly ADP - ribose polymerase (PARP) inhibitors therapy.

Recommendation

- Genetic counseling is strongly recommended to discuss the clinical implications of the test result. Any interpretation provided here should be clinically correlated with available information about the presentation and relevant family history of the patient[2].
- Each of the siblings or children of this patient has a 50% chance of inheriting this mutation. Brothers are just as likely to inherit it as sisters and daughters and sons are equally likely to inherit it. As children's risks of developing cancers associated with a *BRCA1* or *BRCA2* mutation are extremely low, testing for this mutation is not recommended in childhood as it does not impact health or affect medical management.

SNV & Small InDel

Small-scale DNA variations such as single nucleotide variants (SNVs) and small insertions and deletions (InDels) are two common types of genetic mutations where sequences of DNA are changed, inserted, or deleted in an individual.

Variant Interpretation

Based on the specimen used, the test report includes *BRCA1/2* variant interpretation and classification according to the international standards so as to advise treatment options.

LGR

Large Genomic Rearrangements (LGRs) are large-scale DNA structural variations that constitute a significant proportion of *BRCA1/2* mutations in cancer patients. LGR testing enables a more complete investigation on *BRCA1/2* mutations.

Note: All tests carried out by ACT Genomics are conducted in a CAP-certified laboratory. Please consult your physician for any enquiries related to clinical interpretation of the test results. The images used are for illustrative purposes only. The actual products may differ.

CAP ACCREDITED
COLLEGE of AMERICAN PATHOLOGISTS

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