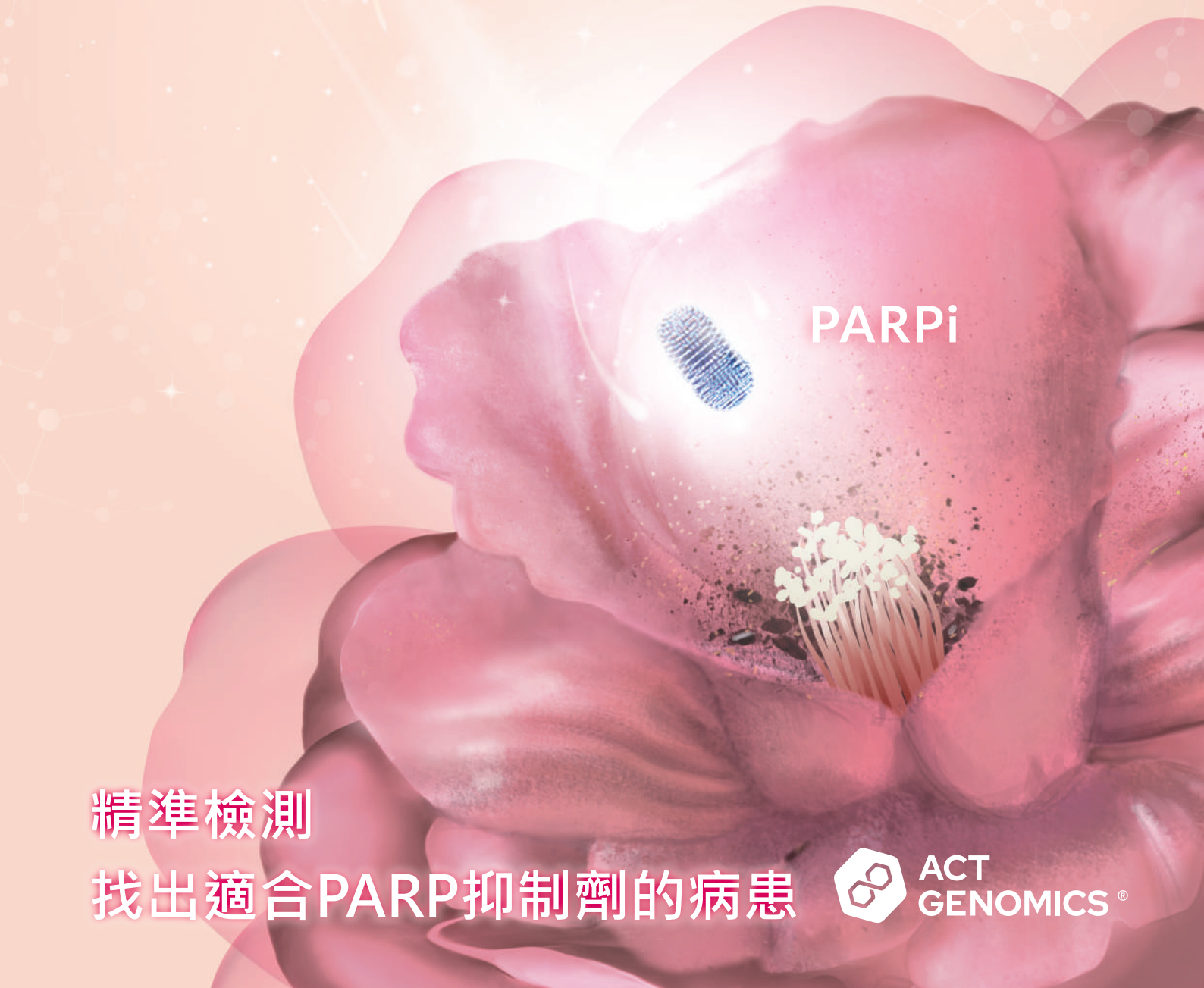
ACT HRD™

帕癌檢®+癌症基因檢測



精準檢測

找出適合PARP抑制劑的病患

ACT GENOMICS®

ACT HRD™ 檢測規格

檢測基因	24 基因
檢測項目[1,2]	• **HRD Status** (由LOH Status是否陽性、*BRCA1/2*是否有致病性突變判定) • **單核苷酸變異、小片段插入缺失、拷貝數變異及*BRCA1/2*大片段基因重組**
靈敏度[3]	100.00% [95% CI: 85.69%, 100.00%]
特異性[3]	90.91% [95% CI: 62.26%, 99.53%]
準確率[3]	97.06% [95% CI: 85.08%, 99.85%]
精準度[3]	95.83% [95% CI: 79.76%, 99.79%]
NGS平均定序深度	≥1000X
推薦適用癌種	卵巢癌、前列腺癌、乳癌...等
使用檢體	石蠟包埋檢體 (FFPE)，5-20片未染色切片 (5 μm / 片)， 組織總表面積 ≥ 125 mm^2，1片H&E染色玻片 (5 μm)
檢測時間	10個工作天 (以認證實驗室收到合格檢體始算)

註：1. 檢測會因生物資訊判定之檢體腫瘤含量(Tumor Purity)之差異而可能無法提供完整資訊。(LOH status需腫瘤含量大於40%CNV, LGR 資訊需腫瘤含量大於30%才能提供)
2. 由於檢測技術限制及個體腫瘤基因差異等因素，即使檢測人員已確實執行標準操作程序，仍可能發生無法提供檢測特定基因或特定生物標記之情形或未發現任何異常。
3. 與美國FDA核准之檢測平台相比HRD Status分析的一致性。

ACT HRD™ 檢測基因

BRCA1	*BRCA2*	*ARID1A*	*ATM*	*ATR*	*ATRX*	*BARD1*	*BRIP1*
CDK12	*CHEK1*	*CHEK2*	*FANCA*	*FANCL*	*FANCM*	*HDAC2*	*NBN*
PALB2	*PPP2R2A*	*PTEN*	*RAD51*	*RAD51B*	*RAD51C*	*RAD51D*	*RAD54L*

* 藍色標籤標記之基因額外檢測LGR

ACT HRD™ 檢測優勢

完整HRD Status

涵蓋*BRCA1/2*、HRR基因外顯子(Exon)及常見剪接區(Splicing Regions)，利用NGS技術，偵測單核苷酸變異 (SNV)、小片段插入/缺失 (Small InDel)、大片段重組 (LGR)與拷貝數變異 (CNV)；更透過專利演算法，呈現LOH Status資訊。

國際完整資料庫

採用國際資料庫gnomAD、1000 Genome、ClinVar、COSMIC及行動基因獨有亞洲族群資料庫，相關分析數據亦已發表於國際期刊。

詳細醫學報告

提供最新AMP Guidelines疾病分級建議、臨床用藥資訊、國際臨床研究文獻及疾病風險資訊等，提供更多臨床判讀資訊。

國際品質認證

檢測皆在美國CAP認證實驗室進行，並獲得台灣TFDA精準醫療分子檢測實驗室(認證編號LDT0001)

異常位點後續確認

針對報告中所示之異常位點，提供個案或家屬之遺傳性後續確認。

註:後續確認之檢測需於檢測前由專業遺傳諮詢師諮詢後執行，且需自負檢測相關費用。

ACTHRD™ 帕癌檢®+癌症基因檢測

提供病患PARP抑制劑用藥資訊

PARP抑制劑(PARP Inhibitor)在過去幾年的癌症臨床研究中，陸續取得了重大突破。隨著FDA的核准，罹患卵巢癌、乳癌、前列腺癌、胰臟癌等的病患能藉由基因檢測得知自身是否適合使用PARP抑制劑作為治療方式。

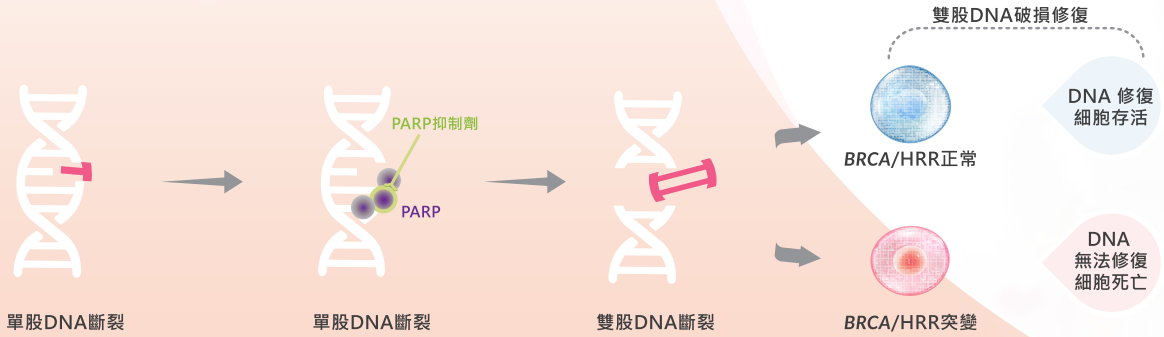
HRR基因異常導致HRD

若細胞屬於同源重組修復缺失(Homologous Recombination Deficiency, HRD)，其DNA無法正常修復，對細胞會產生嚴重的影響。因為細胞中的DNA在自然情況下可能受到許多因素影響而造成損傷，這些損傷累積後可能造成雙股DNA破損(DNA Double-strand Break, DSB)。當雙股DNA破損發生時，細胞需透過同源重組修復機制(Homologous Recombination Repair, HRR)才能將雙股DNA正確無誤的修復[1,2,3]。整個同源重組修復機制中有許多基因參與，除了常被提及的*BRCA1*和*BRCA2*外，*ATM*、*CHEK2*、*PALB2*、*RAD51*等基因也參與在其中；當這些同源重組修復基因發生變異或表現量的調控異常而失去正常功能時，會導致異質性缺失(Loss of Heterozygosity, LOH)，造成基因體的異常或不穩定。因此利用檢測同源重組修復基因變異或是LOH，可做為評估癌細胞是否帶有HRD的現象[4]。

PARP抑制劑能用於治療HRD癌症

PARP為一種DNA修復酶，負責DNA雙股螺旋中的單股DNA斷裂修復(Single Strand Break Repair, SSBR)，在DNA受損的早期，即會啟動細胞中對DNA受損的修補反應。

一般情況下，癌細胞單股DNA斷裂，可經由PARP進行修復；但在具有*BRCA*基因或HRR基因變異的病患，在PARP抑制劑作用下，單股DNA斷裂會因為無法修復而進一步造成雙股DNA斷裂，並且也無法修復，最後造成癌細胞死亡。實驗室數據與臨床試驗結果指出，在這一類型病患中使用PARP抑制劑可有效達到疾病控制[5]。

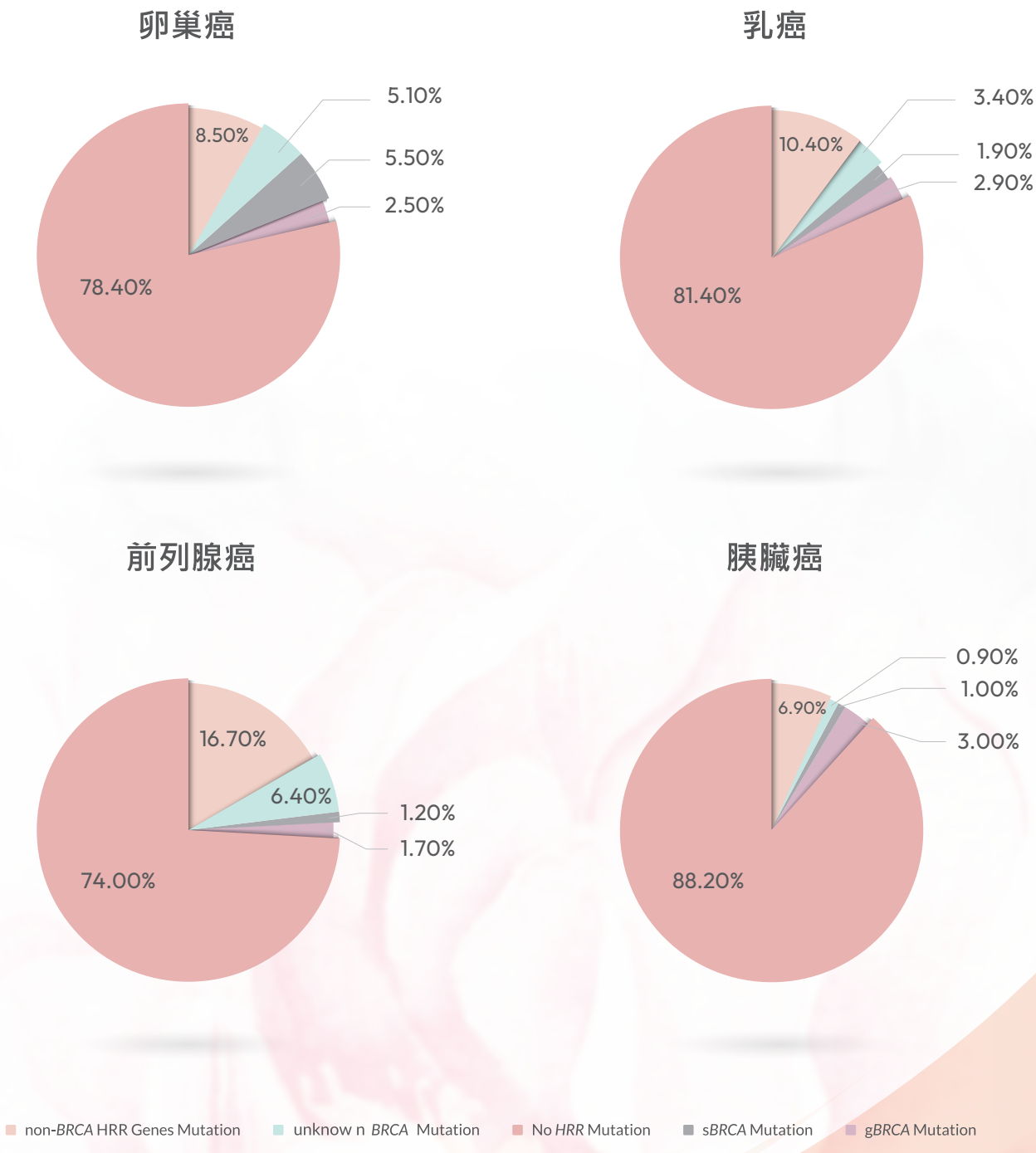


圖一：*BRCA*/HRR基因異常導致細胞合成致死[7,8,9,10]

1.Venkitaraman AR. Annu Rev Pathol 2009; 4: 461-487.
2.Li X, Heyer WD. Cell Res. 2008;18:99-113.
3.Lord CJ, Ashworth A. Nat Rev Cancer. 2016;16:110-120.
4.Watkins JA, Irshad S, Grigoriadis A, Tutt AN. Breast Cancer Res. 2014;16:211
5.Hartwell LH, Szankasi P, Roberts CJ, et al. Science 1997; 278: 1064-1068.
6.Turner, N., Tutt, A. & Ashworth, A. Nat. Rev. Cancer 4, 814–819 (2004).
7.Venkitaraman AR, . Science 2014; 343: 1470-1475
8.Livraghi L, Garber JE. BMC Med 2015; 13:188.
9.Farmer H, McCabe N, Lord CJ, et al.Nature 2005; 434: 917-921
10.Bryant HE, Schultz N, Thomas HD, et al. Nature 2005; 434: 913-917.

HRD與癌症有高度關連性

目前針對相關生物標記中，研究最為透徹的為*BRCA*相關基因突變，但因HRR修復機制相關的基因至少有數十個，因此僅針對*BRCA*進行檢測是不夠的。後續於臨床研究中，在沒有*BRCA*基因突變的腫瘤中，亦發現具有和*BRCA*基因變異相似的表現型(Phenotype)，因此PARP抑制劑於這類型癌症治療當中，重要性日漸提升。



Source: Cai C, Dettman EJ, Zhou W, et al. Prevalence of homologous recombination biomarkers in multiple tumor types: an observational study. Future Oncology. 2024. doi:10.1080/14796694.2024.2367957.

ACTHRD™ 報告

ACTHRD™ Report

Identifier
Project ID:
Report No.:
Report Date:

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

ABOUT ACTHRD™

The test is a next-generation sequencing (NGS) based assay to detect single nucleotide variants (SNVs), small insertions and deletions (InDels), copy number alterations (loss) (CNA-loss), large genomic rearrangements (LGRs) in the *BRCA1* and *BRCA2* genes, and analyze the genomic loss of heterozygosity (LOH) status using DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens. Results of the test are used as an aid in identifying cancer patients with positive homologous recombination deficiency (HRD) status for treatment with PARP inhibitors. Additionally, the test is intended to provide tumor profiling on SNVs, InDels, and CNA-loss of 22 homologous recombination repair (HRR) genes for use by qualified health care professionals in accordance with professional guidelines, and is not conclusive or prescriptive for labeled use of any specific therapeutic products

Report Summary for Actionable Variants/Biomarkers

Homologous Recombination Deficiency (HRD) Status		
HRD Status	**Gene/Biomarker**	**Result**
Positive	*BRCA1*	Negative
	BRCA2	Positive
	Loss of heterozygosity (LOH)	Positive (0.57)

* Homologous Recombination Deficiency (HRD) Positive= Either BRCA1/2 mutant or LOH positive

S Sensitive R Resistant

Variants/Biomarkers with Clinical Significance (Target Therapy)		
Genomic Alterations	**Evidence Level 1, 2 (FDA-approved, NCCN guideline)**	**Evidence Level 3A, 3B, 4 (Others)**
LOH positive	S Niraparib, Olaparib	S Rucaparib
BRCA2 Y1655*	S Niraparib, Olaparib, Rucaparib	S Talazoparib
BRCA2 Heterozygous deletion	S Niraparib, Olaparib, Rucaparib	S Talazoparib

Note:
- The therapeutic agents and possible effects to a given drug are based on mapping the variants/biomarkers with ACT Genomics clinical knowledge database. The mapping results only provide information for reference, but not a medical recommendation.
- Please refer to the corresponding sections for more detailed information about genomic alteration and clinical relevance listed above.

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ACT Genomics' laboratory is accredited by CAP (CAP number: 9028096).
ACT Genomics only provides a technical report of the test; please consult a specialist physician to determine the appropriate clinical solution and follow the instructions of the physician. The results are only valid for the tested sample(s).
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Email: service@actgenomics.com T: +886-2-2795-3660 F: +886-2-2795-5016

HRD Status

透過判別*BRCA1*、*BRCA2*、及LOH Status (Loss of Heterozygosity Status)，即能判別腫瘤HRD之情形，提供進一步用藥資訊。

單核苷酸變異&小片段插入缺失

小範圍的基因突變如核苷酸(Nucleotide)單一點突變或小片段插入缺失所導致HRR基因喪失DNA修復功能。並依照國際準則給予不同等級之判別。

拷貝數變異

分析拷貝數變異，辨別導致基因功能缺失的基因異型/同型合子缺失(Heterozygous/Homozygous Deletion)。

ACTHRD™ Report

Identifier
Project ID:
Report No.:
Report Date:

Testing Results of Variants/Biomarkers with Clinical Relevance

Homologous Recombination Deficiency (HRD) Status
Positive

* Homologous Recombination Deficiency (HRD) Positive= Either BRCA1/2 mutant or LOH positive

Single Nucleotide and Small InDel Variants		
Gene Alterations	**Allele Frequency**	**Classification**
BRCA2 c.4965del (Y1655*)	68.7%	Deleterious

Copy Number Alterations			
Gene	**Chromosome**	**Variation**	**Copy Number**
BRCA2	Chr13	Heterozygous deletion	1

Large Genomic Rearrangements	
Gene	**Alteration**
Not detected	

Loss of Heterozygosity Status	
LOH Status	**LOH Score**
Positive	0.57

Note:
- CNA, LGR, and LOH status in the tumor were determined based on [redacted] tumor purity (calculated by NGS/estimated by the pathologist).
- Samples with tumor purity lower than 40% are unable to be analyzed for the LOH status.
- Samples with tumor purity lower than 30% are unable to be analyzed for CNA and LGR.
- The homologous recombination deficiency (HRD) status is defined as deleterious or suspected deleterious alterations of *BRCA1* and *BRCA2*, and/or LOH status positive. The threshold for LOH status positive is set at a score ≥ 0.4. Of note, the HRD definition is in accordance to the approved therapeutic product labeling in ovarian cancer and not in other cancer types.
- Only deleterious or suspected deleterious variants are listed in this section. For variants of unknown significance (VUS), please refer to Supplementary Information on Testing Results. Variants classified as benign, likely benign, and synonymous variants are not reported.

Supplementary Information for Therapeutic Implications

Targeted Therapies		
Genomic Alterations	**Therapies**	**Evidence Level**
LOH positive	S Niraparib, Olaparib	1
BRCA2 Y1655*	S Niraparib, Olaparib, Rucaparib	1
BRCA2 Heterozygous deletion	S Niraparib, Olaparib, Rucaparib	1
BRCA2 Y1655*	S Talazoparib	3A
BRCA2 Heterozygous deletion	S Talazoparib	3A
LOH positive	S Rucaparib	3B

Therapies associated with benefit or lack of benefit are based on biomarkers detected in this tumor and published evidence in professional guidelines or peer-reviewed journals.

Level	Description
1	FDA-recognized biomarkers predictive of response or resistance to FDA-approved drugs in this indication
2	Standard care biomarkers (recommended by the NCCN guideline) are predictive of response or resistance to FDA-approved drugs in this indication
3A	Biomarkers predictive of response or resistance to therapies approved by the FDA or NCCN guideline in a different cancer type
3B	Biomarkers that serve as inclusion criteria for clinical trials (minimal supportive data required)
4	Biomarkers that show plausible therapeutic significance based on small studies, few case reports, or preclinical studies

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*BRCA*大片段基因重組

除小範圍的基因突變外，*BRCA1/2*基因由於外顯子缺失或重複所形成的大片段基因重組(Large Genomic Rearrangement, LGR)於基因突變佔有相當比例。

LOH Status

專利運算法分析近九千個SNPs(Single Nucleotide Polymorphism)得知腫瘤組織中LOH程度，用來判斷腫瘤組織的HRD狀態。

治療建議

根據國際資料庫及臨床文獻，給予後續用藥治療等級建議。

註：行動基因所有檢測皆於CAP合格認證實驗室進行檢測，並依結果出具技術檢測報告。關於報告的臨床解釋及相關醫療問題，請向專業醫師諮詢相關建議。以上圖像皆為說明用途，實際圖像可能與上述有所不同。

CAP ACCREDITED
COLLEGE of AMERICAN PATHOLOGISTS

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