台灣婦產科醫學會
Taiwan Association of Obstetrics and Gynecology

臺中榮民總醫院
Taichung Veterans General Hospital

HRD 的充分了解

許世典
台中榮民總醫院/婦女醫學部/婦癌科

婦產科醫學會2023年年會

婦癌symposium 16:10-16:30

座長：王鵬惠教授，張志隆教授

台中裕元花園酒店

12/Aug/2023

Disclosure

- nil

Outline

- Introduction
- DNA修復異常與癌症治療
- HRD原理
- Real world data

Introduction

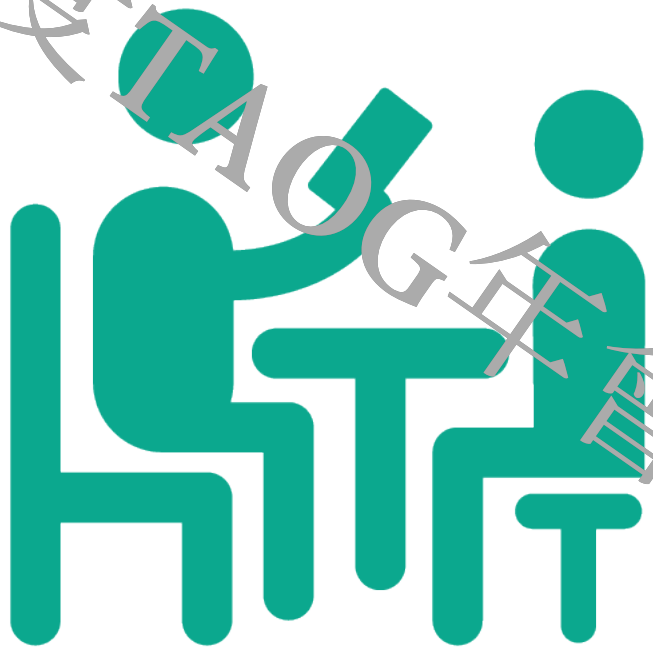
以往癌症治療

診斷

影像攝影

病理切片

討論組織學
型態與分期
決定治療



治療

手術治療

化療/荷爾蒙?

放射線治療?

利用生物標記進行癌症治療

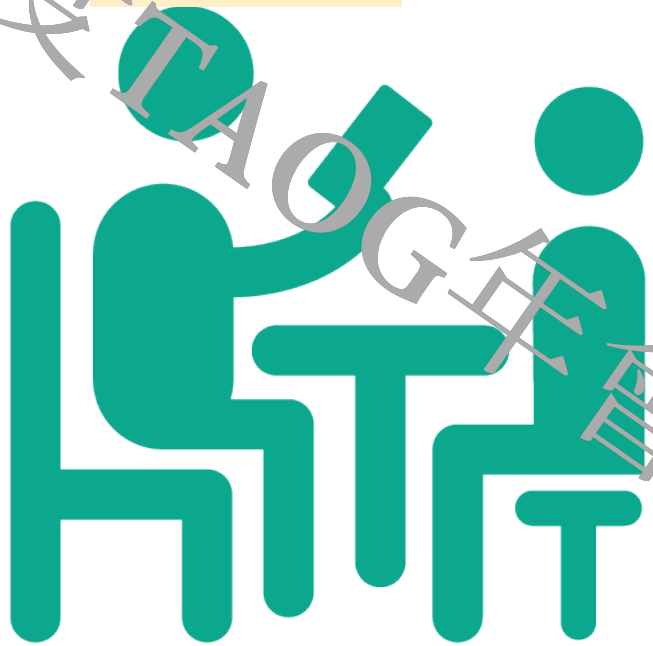
診斷

影像攝影

病理切片
（免疫染色）

FISH
基因檢測
分生檢測

討論分子生物學檢測報告與其臨床意義



治療

標靶藥物?

手術治療

化療/荷爾蒙?

放射線治療?

免疫療法?

生物標記的應用

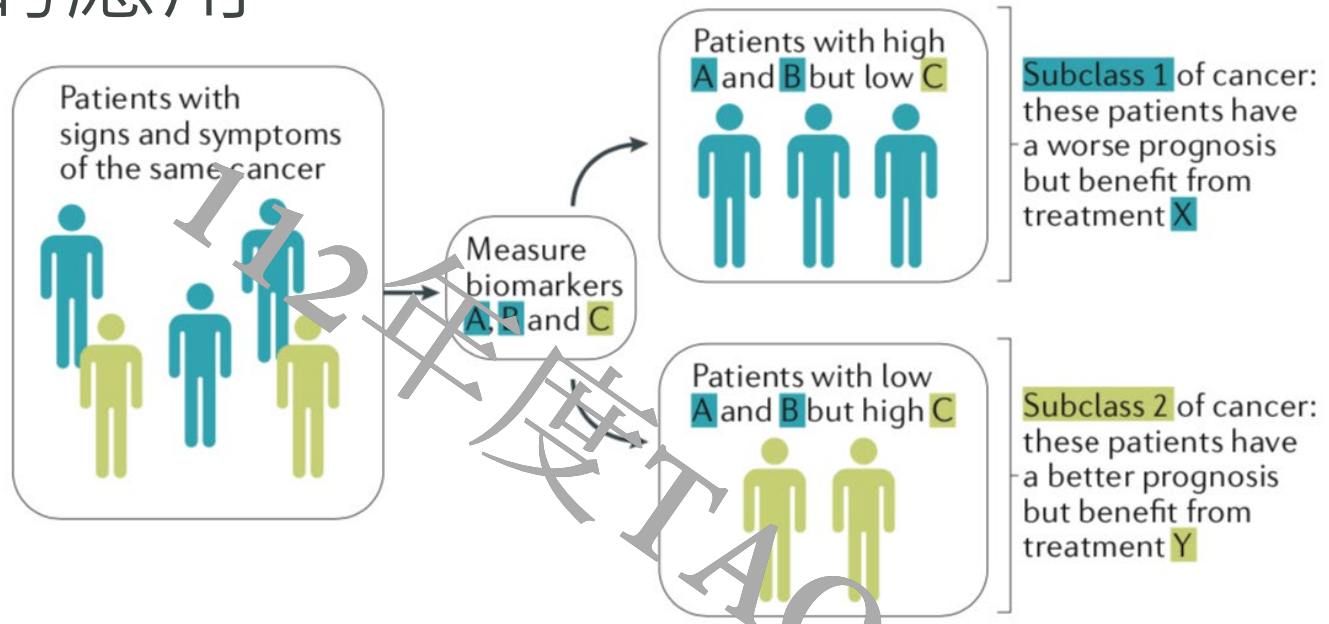
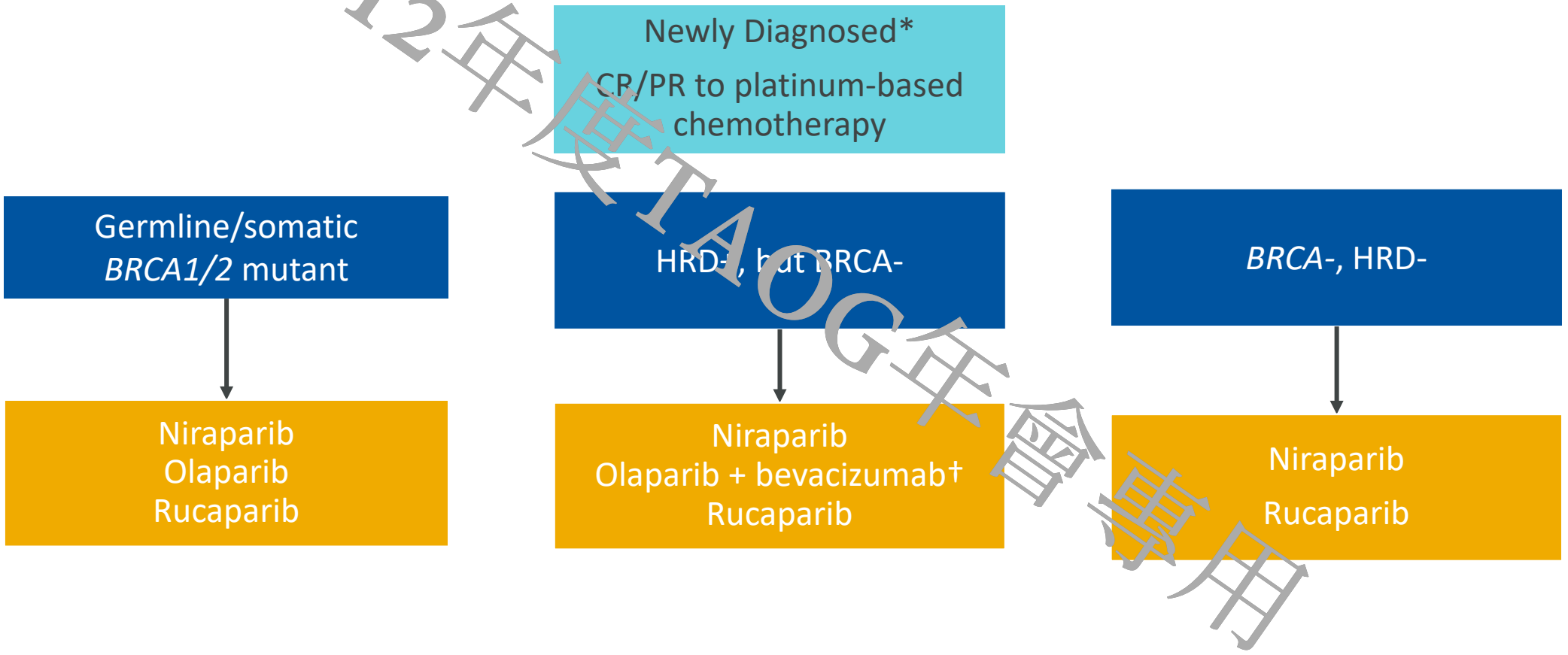


Figure 1 | **Classifying patients into new, specific taxa.** Patients with the same signs and symptoms of cancer often have different outcomes. The precision medicine approach provides a research strategy to develop biomarkers that can be used to classify patients with the same cancer into finer taxa (subclass 1 versus subclass 2) by biomarkers that predict prognoses derived from the synthesis of large amounts of data to identify discriminating biomarkers. For example, patients in subclass 1 who have a worse prognosis (that is, have biomarkers that are associated with poor survival) may be given a more aggressive treatment (treatment X) versus those in subclass 1 who have a better prognosis (that is, have biomarkers that are associated with good outcome) and require a less aggressive therapy (treatment Y). Additionally, the converse may be true where individuals with a worse prognosis are provided less aggressive therapy if no benefit from aggressive treatment has been observed for this subclass.

選擇對的人
做對的治療

分類(特徵)
有/無
高/低

Summary of Guideline Recommendations for PARP Inhibitors as Frontline Maintenance in Ovarian Cancer



Tew. JCO. 2022;40;3878. Niraparib PI. Olaparib PI. Rucaparib PI. Monk. JCO. 2022;40:3952.

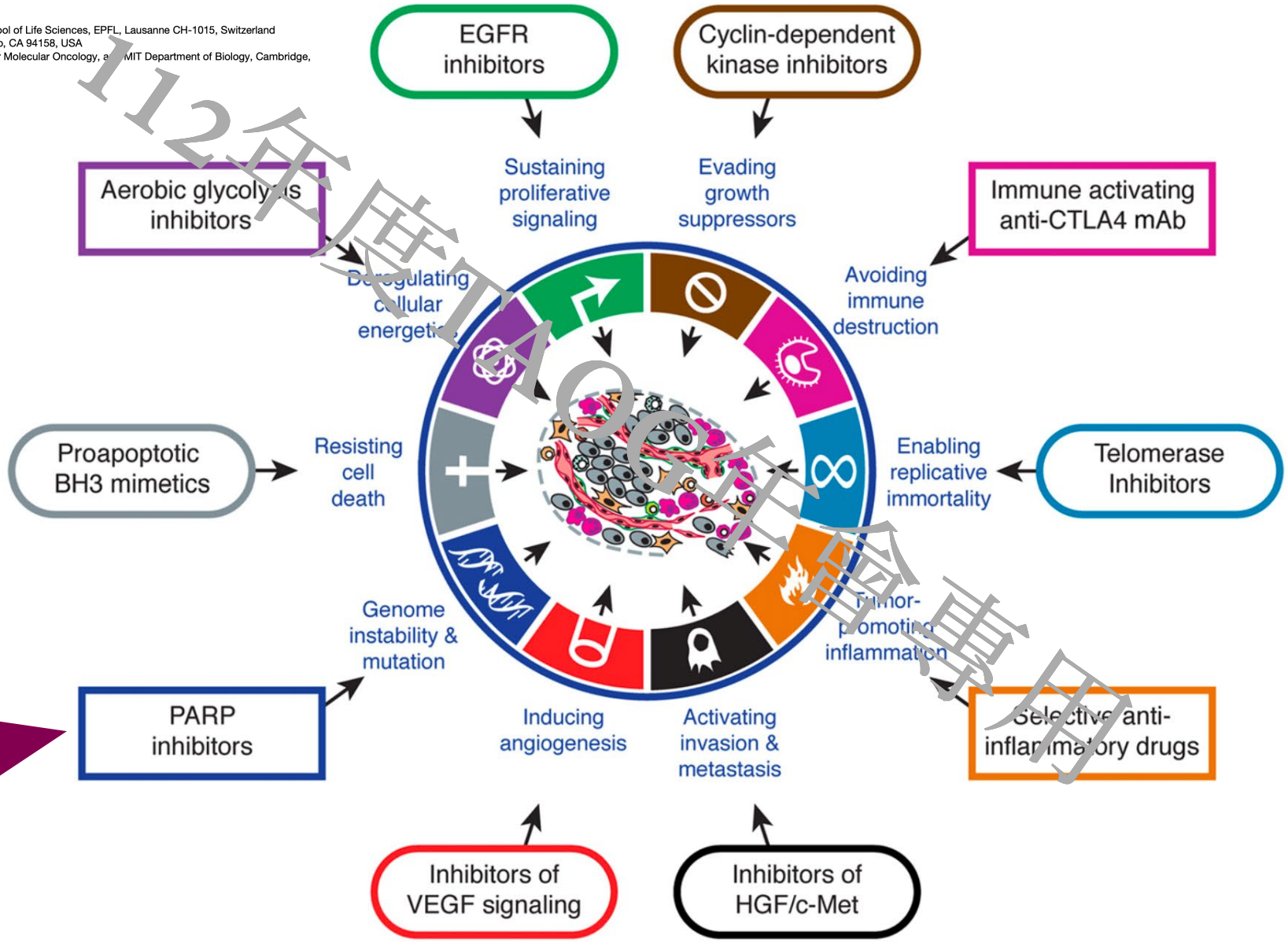
DNA修復異常與癌症治療

Cell

Leading Edge
Review

Hallmarks of Cancer: The Next Generation

Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]
[1]The Swiss Institute for Experimental Cancer Research (ISREC), School of Life Sciences, EPFL, Lausanne CH-1015, Switzerland
[2]The Department of Biochemistry & Biophysics, UCSF, San Francisco, CA 94158, USA
[3]Whitehead Institute for Biomedical Research, Ludwig/MIT Center for Molecular Oncology, and MIT Department of Biology, Cambridge, MA 02142, USA
*Correspondence: dh@epfl.ch (D.H.), weinberg@wi.mit.edu (R.A.W.)
DOI 10.1016/j.cell.2011.02.013



今天的主題
針對卵巢癌
DNA修補的
生物指標

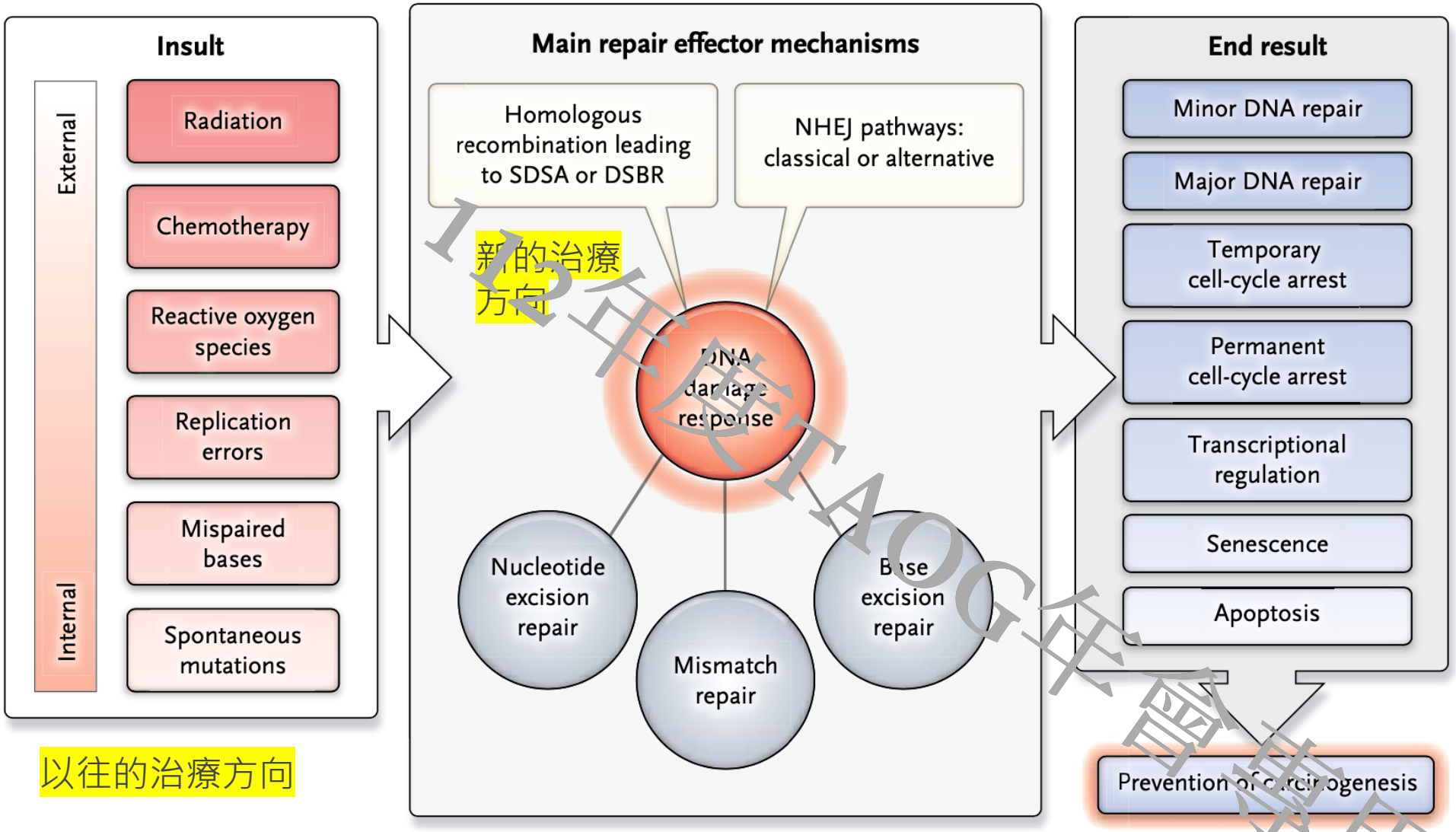
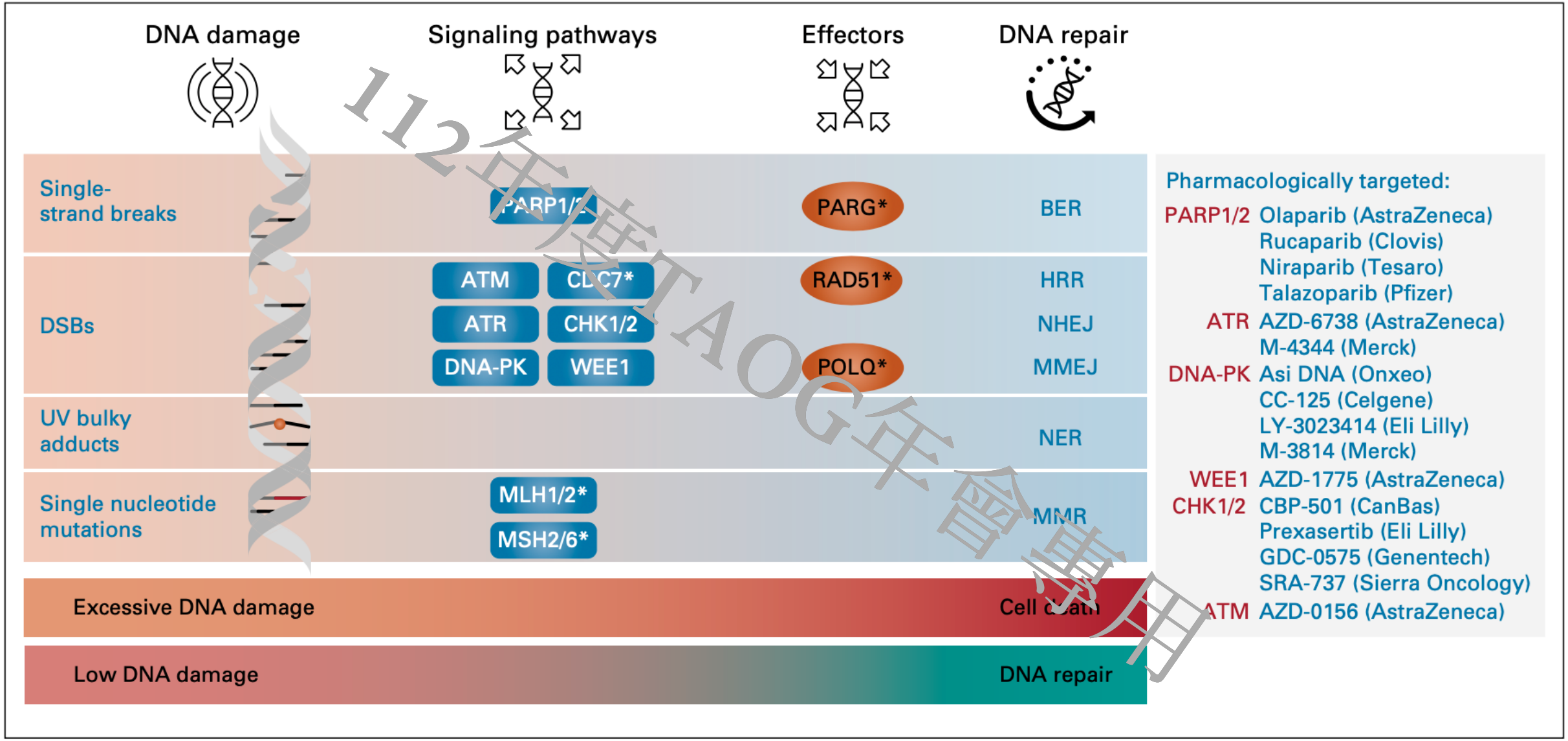


Figure 2. Overview of DNA-Damage-Response Pathways in Competent Human Cells.

After either internal or external insults to genomic integrity, differential activation of repair pathways induces heterogeneous end responses that are dependent on the degree of damage and ability to repair DNA. Homologous recombination of double-strand DNA breaks can result in activation of either the double-strand break repair (DSBR) pathway or the synthesis-dependent strand annealing (SDSA) pathway. The nonhomologous end-joining (NHEJ) pathway can be divided into the classic and alternative pathways. The pathways for base excision repair, nucleotide excision repair, and mismatch repair are also pivotal mediators that minimize the effects of deleterious DNA insults.

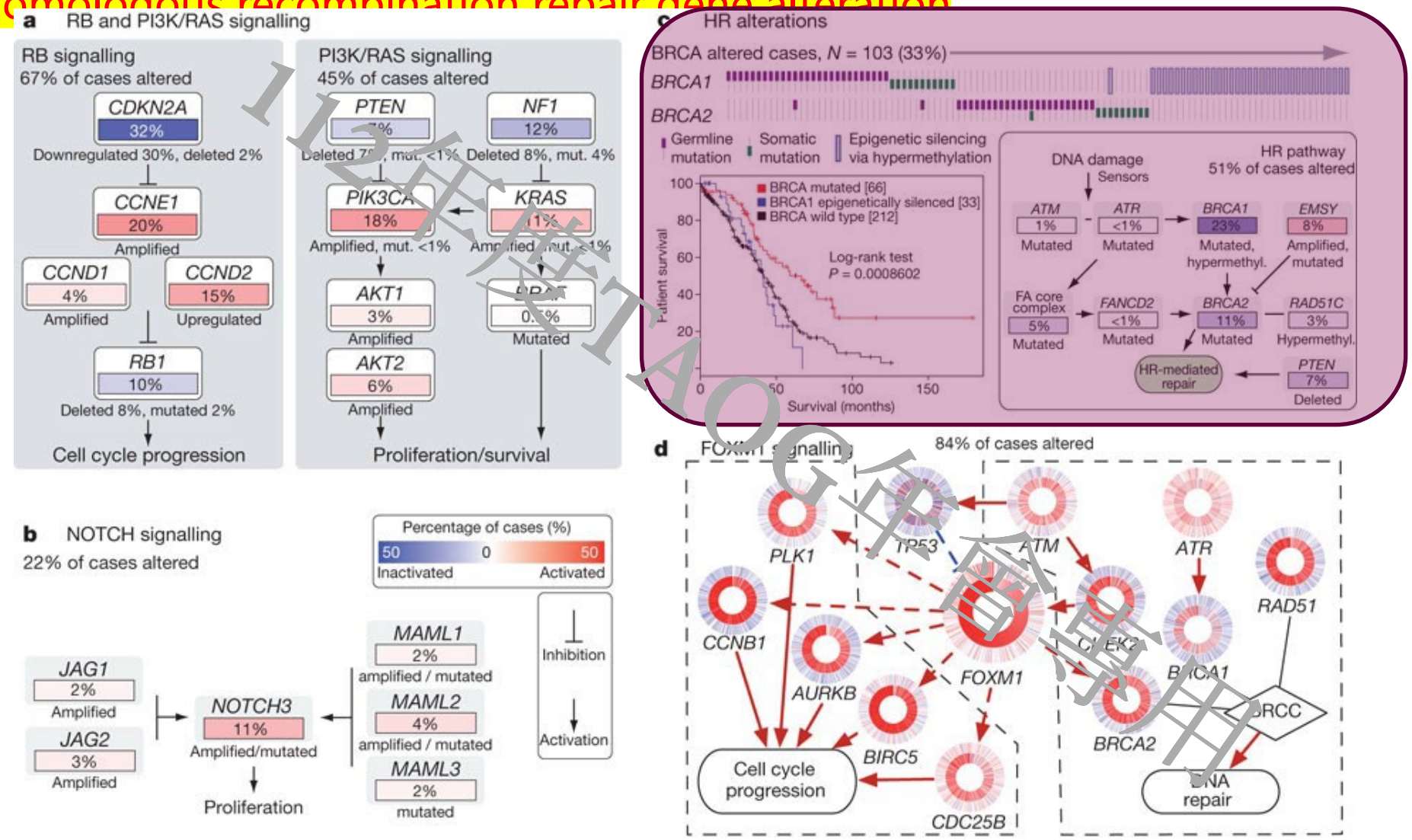


J Clin Oncol 37:2257-2269. © 2019 by American Society of Clinical Oncology

TCGA: High grade serous ovarian cancer(最常見的上皮性卵巢癌）的基因表現

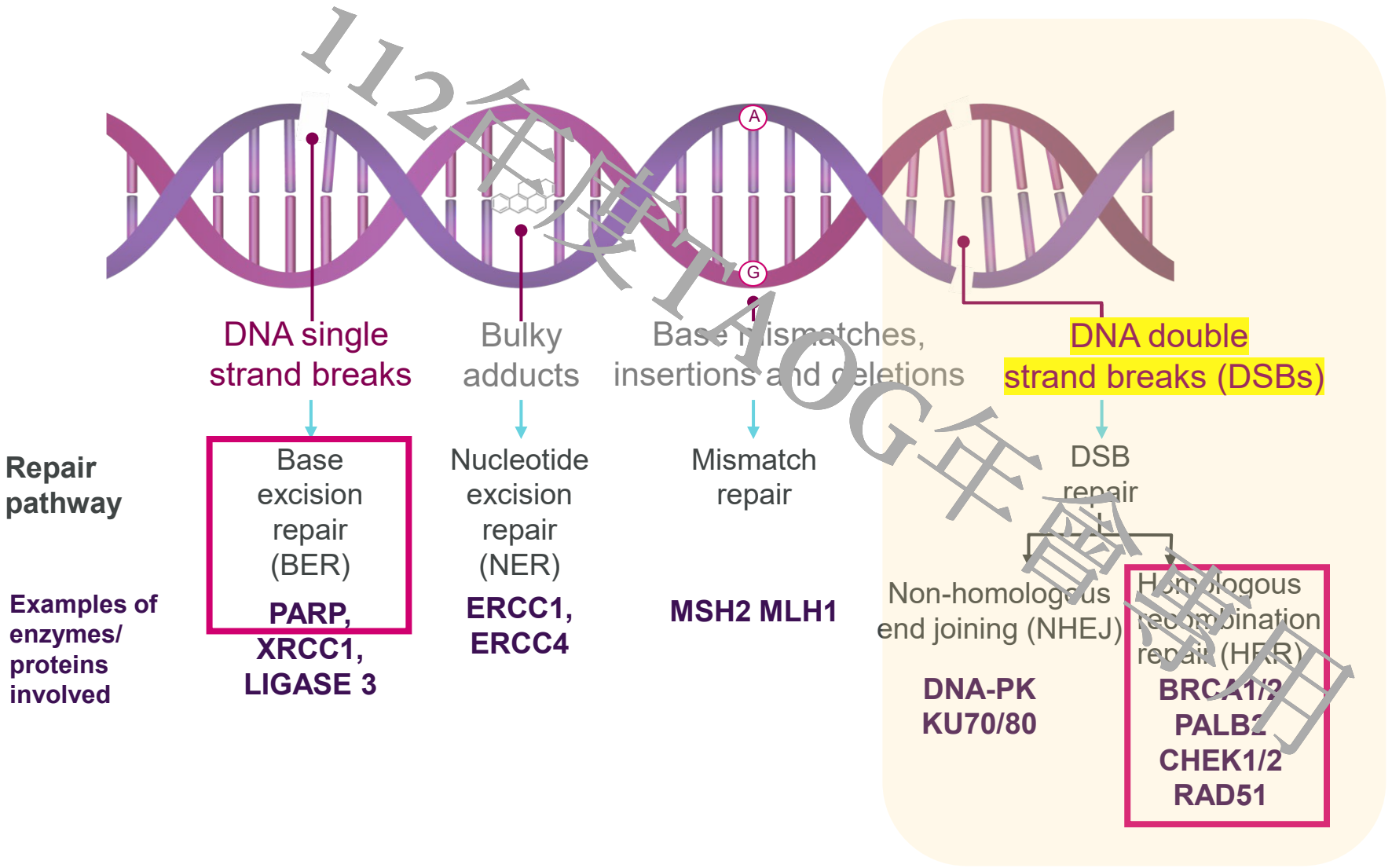
33%有Homologous recombination repair gene alteration

nature



D Bell et al. Nature 474, 609-615 (2011) doi:10.1038/nature10166

DNA damage response(DDR)



- HRR uses a homologous DNA template to repair DSB（可用另一條同源DNA做模板修復）
- It is an error-free DNA repair pathway（可正確修復）
- 有homologous recomplation repair缺失的細胞只能靠NHEJ(直接黏起來）

BER=base excision repair; DDR=DNA damage response; DNA=deoxyribonucleic acid; DSB=double stand break; HRR=homologous recombination repair; NER=nucleotide excision repair; NHEJ=non-homologous end joining

Figure adapted from: 1. Lord CJ, and Ashworth A. Nature. 2012;481:287–294

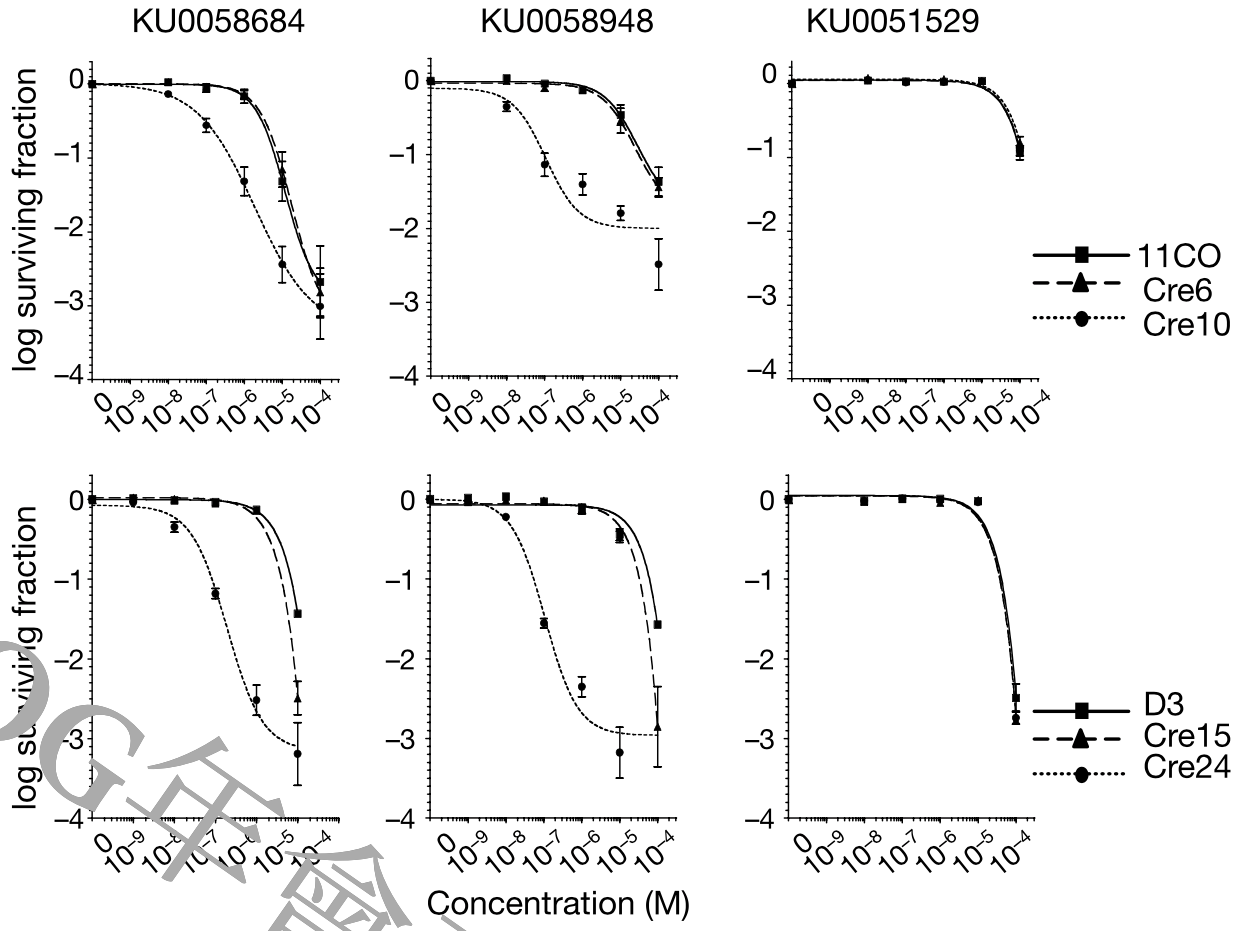
Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase

Helen E. Bryant[1], Niklas Schultz[2], Huw D. Thomas[1], Kayan M. Parker[1], Dan Flower[1], Elena Lopez[1], Suzanne Kyle[3], Mark Meuth[1], Nicola J. Curtin[3] & Thomas Helleday[1,2]

Targeting the DNA repair defect in *BRCA* mutant cells as a therapeutic strategy

Hannah Farmer[1,2]*, Nuala McCabe[1,2]*, Christopher J. Lord[2]*, Andrew N. J. Tutt[2,3], Damian A. Johnson[2], Tobias B. Richardson[2], Manuela Santarosa[2]†, Krystyna J. Dillon[4], Ian Hickson[4], Charlotte Knights[4], Niall M. B. Martin[4], Stephen P. Jackson[4,5], Graeme C. M. Smith[4] & Alan Ashworth[1,2]

NATURE | VOL 434 | 14 APRIL 2005

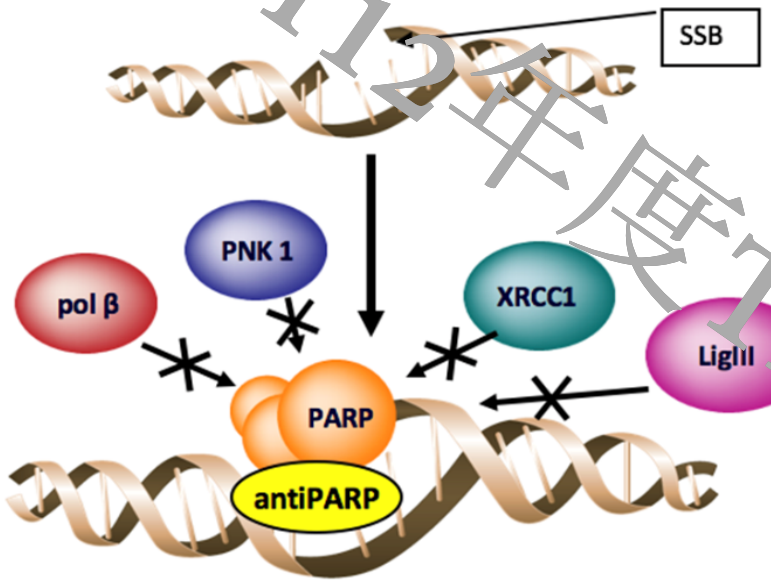


有BRCA缺陷的細胞（homologous recombination repair deficiency的細胞）

若抑制 PARP蛋白，因單股DNA損傷無法修復，累積很多的雙股DNA缺失，又只能靠NHEJ修復，細胞就會凋亡

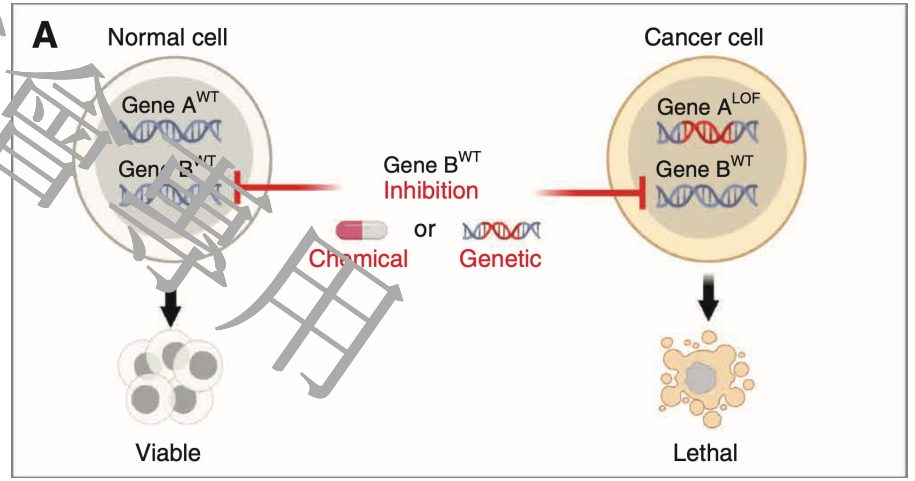
PARP INHIBITORS

Poly(ADP-ribose) polymerase and DNA Repair

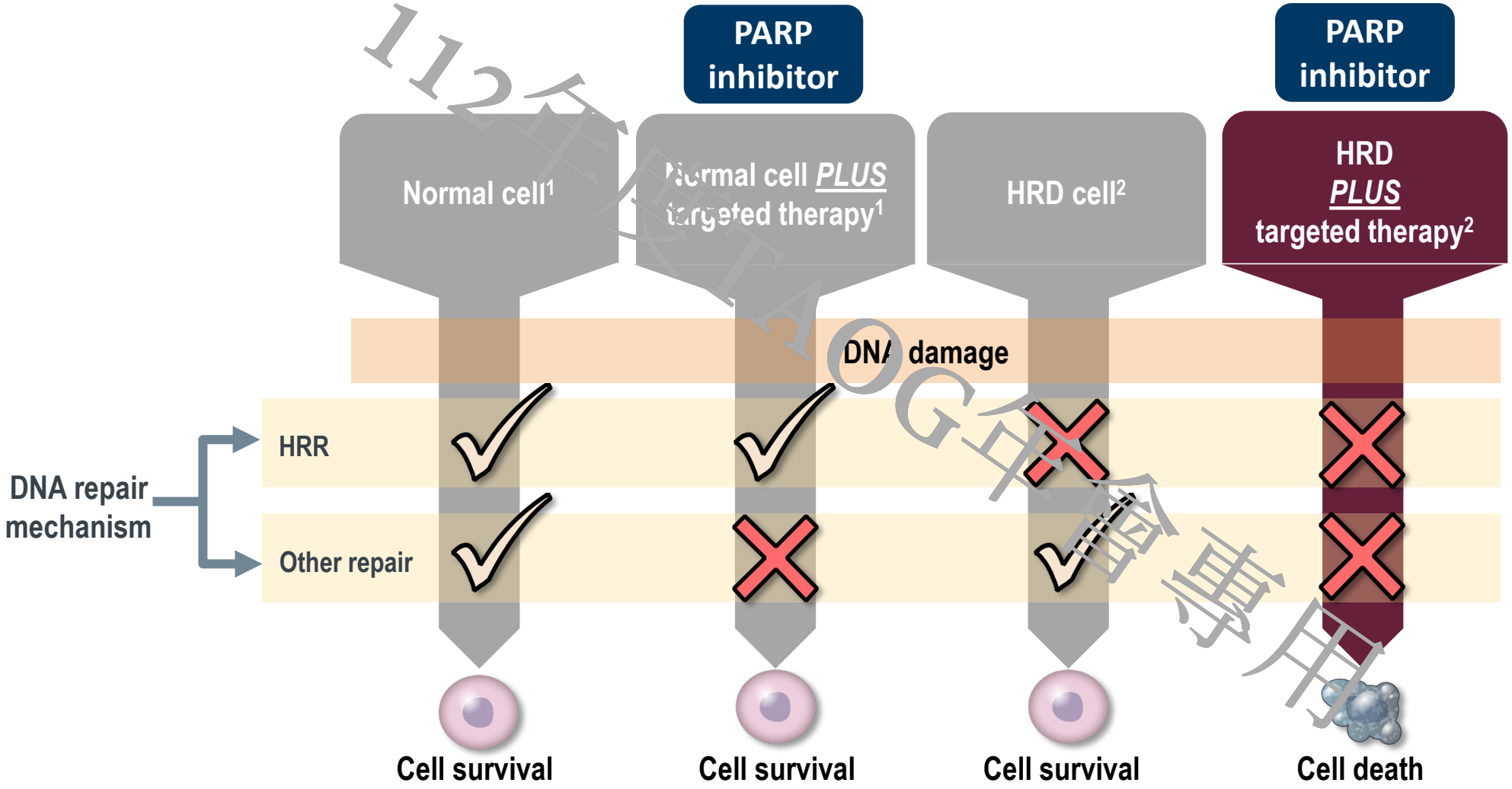


PARP inhibitor→
阻斷單股DNA修復，
增加雙股DNA斷裂
→無法準確修補→
細胞死亡

- PARP is a key regulator of DNA damage repair processes
- Involved in DNA base-excision repair (BER)
- Binds directly to DNA damage
- Produces large branched chains of poly(ADP-ribose)
- Attracts and assists BER repair effectors



Synthetic lethality occurs when two separate non-lethal defects become lethal when combined[3,4]



DNA, deoxyribonucleic acid; HR, homologous recombination; HRR, homologous recombination repair; PARP, poly (ADP-ribose) polymerase

1. Walsh CS. *Gynecol Oncol.* 2015;137(2):343-350. 2. Konecny GE, et al. *Br J Cancer*. 2016;115:1157-1173. 3. George A, et al. *Nat Rev Clin Oncol*. 2017;14(5):284-296.

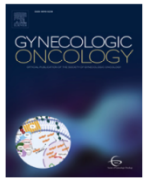
HRD(homologous recombination deficiency)原理與應用

Gynecologic Oncology 164 (2022) 221–230

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno



Probability of detecting germline *BRCA1/2* pathogenic variants in histological subtypes of ovarian carcinoma. A meta-analysis

Vera M. Witjes [a], Majke H.D. van Bommel [b], Marjolijn J.L. Ligtenberg [a,c], Janet R. Vos [d], Marian J.E. Mourits [e], Margreet G.E.M. Ausems [f], Joanne A. de Hullu [b], Tjalling Bosse [g], Nicoline Hoogerbrugge [a,*]

Data are limited on the use of maintenance parpi in LCOC（ less common ovarian cnacer)

只有high grade serous csrcinoma病人比較多有BRCA mutation

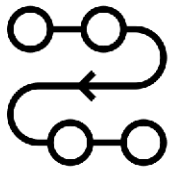
Table 2
Meta-analyses of proportion germline *BRCA1/2* PVs per histological subtype of OC.

Histology	Number of studies	Positive	Total	Pooled proportion (%)	95% CI (%)	Prediction Interval (%)[a]	Hetero-geneity (I^2)	Numbers needed to test to find 1 PV (95% CI)
High-grade serous	28	1738	7914	22.2	19.6 to 25.0	11.6 to 38.2	88%	5 (4 to 6)
Carcinosarcoma	10	9	77	11.9	5.8 to 22.6	3.6 to 32.3	0%	9 (5 to 18)
Endometrioid	27	67	764	5.8	3.3 to 9.9	1.0 to 26.8	0%	18 (11 to 31)
Low-grade serous	23	34	422	5.2	2.3 to 11.3	0.8 to 27.0	0%	20 (9 to 44)
Clear cell	27	29	794	3.0	1.6 to 5.6	0.0 to 48.4	17%	34 (18 to 63)
Mucinous	17	11	244	2.5	0.6 to 9.6	0.1 to 31.4	0%	40 (11 to 167)
Other	25	19	272	7.0	4.5 to 10.7	4.4 to 10.9	0%	15 (10 to 23)

[a] Prediction interval reflects the range in which proportions are expected to be found in future research.

Terminology consistent with community language, labels and guidelines

It is important to distinguish between phenotype and test



Homologous recombination repair (HRR): the cellular mechanism to repair DNA double strand breaks

細胞雙股DNA修復

Homologous recombination deficiency (HRD): the phenotype of a cell/tumor that has impaired ability to conduct HRR (for example due to loss of function of genes involved in the HRR pathway)

雙股DNA修復有問題

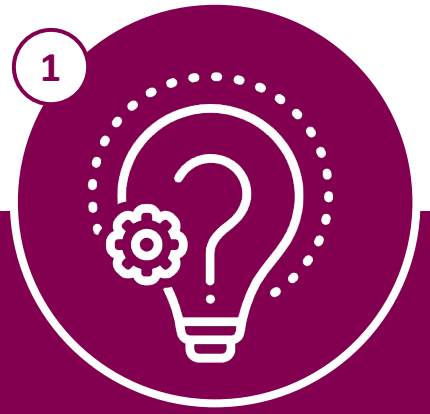
Genomic instability test: a molecular diagnostic test to assess HRD phenotype (for example the Myriad myChoice® CDx test)

檢測雙股DNA修復有問題的方法

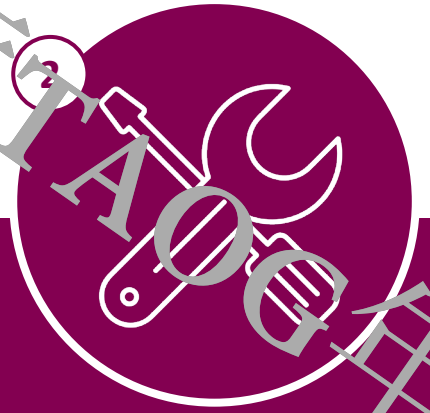
HRD-positive: a tumor which is identified as HRD based on a molecular diagnostic test (for example a genomic instability test)
HRD-negative: a tumor which is identified as HRD-negative based on a molecular diagnostic test

Genomic instability in the context of HRD testing in Ovarian Cancer refers to genomic alterations resulting from homologous repair deficiency (HRD) and not microsatellite instability resulting from mismatch repair (dMMR).

Three approaches to identify HRD



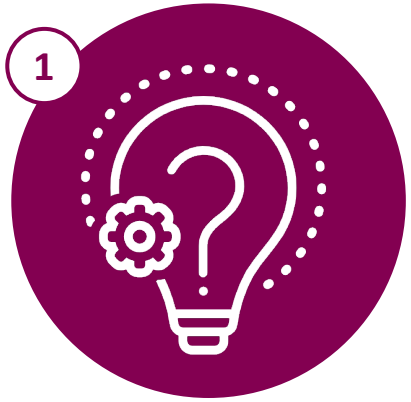
Cause of HRD



Function of HRR

Effect of HRD

Approach 1: Cause of HRD



Cause of HRD

Causes of HRD

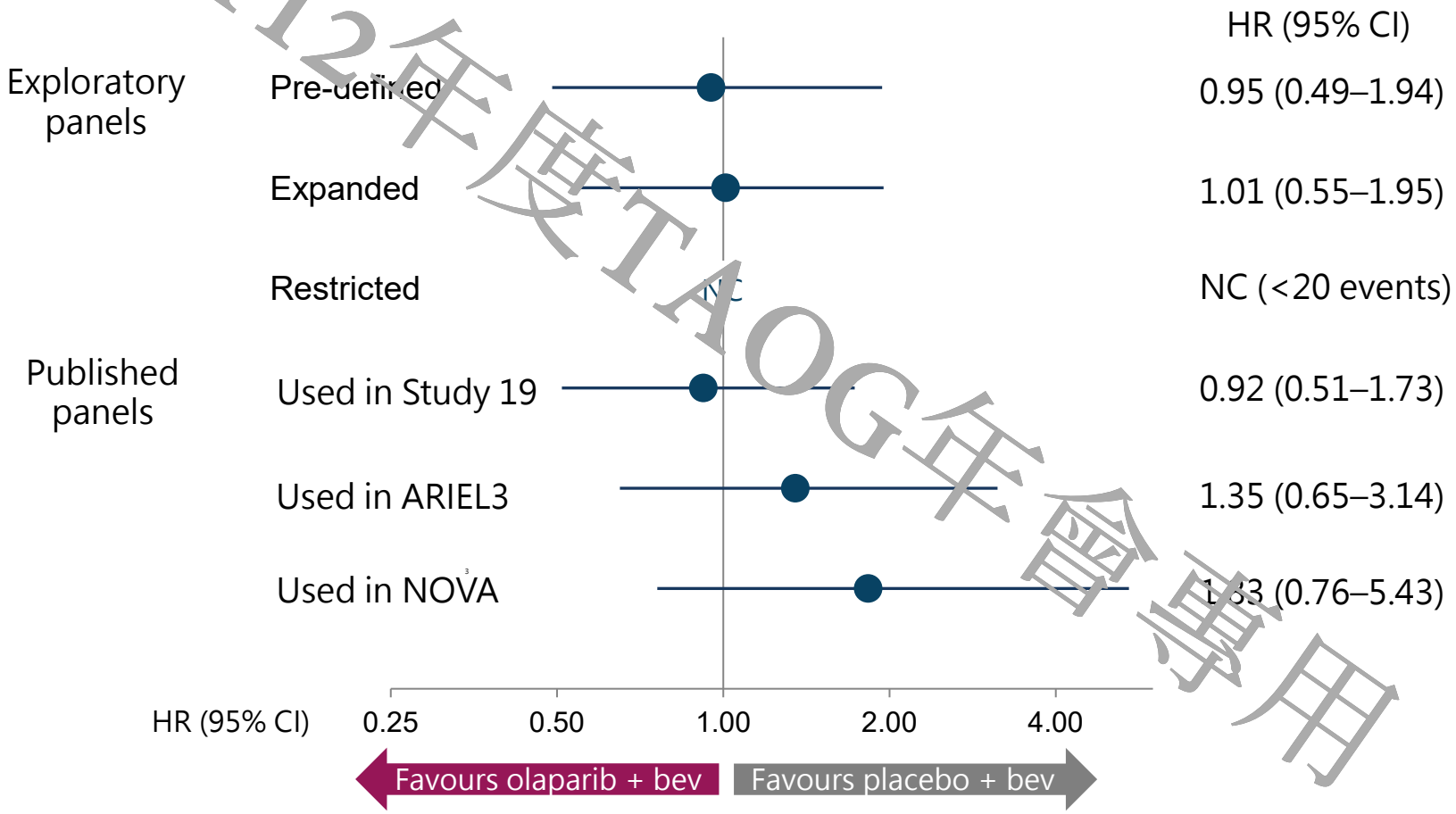
*BRCA1/2*m	HRRm Gene panels
Germline / Tumor	• Loss of function of key HRR genes (tumor test)
• Including point mutation / InDel detected by NGS	• 15 genes in AZ panel: *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L*
• Large DNA deletion detected by MLPA	

1. O'Kane GM et al. Trends Mol Med. 2017;23(12):1121-1137. 2. Hoppe MM, et al. J Natl Cancer Inst. 2018;110(7):704-713

TABLE 2. Known Deleterious Homologous Recombinant Deficiency Gene Frequencies in Ovarian Cancer

HR-Pathway Gene	Observed Frequency All Epithelial Ovarian Cancer (%)	Observed Frequency High-Grade Ovarian Cancer (%)	References
RAD51C	0.41–2.9	1.9	Walsh et al[8], Pennington et al[36], Minion et al[83], Cunningham et al[84], Song et al[85]
RAD51D	0.35–1.1	0.95	Pennington et al[36], Cancer Genome Atlas Research Network[38], Song et al[85]
RAD51B	0.06	0.95	Cancer Genome Atlas Research Network[38], Song et al[85]
RAD50	0.2–1.0	—	Walsh et al[8], Minion et al[83]
RAD54L	—	0.5	Kristeleit et al[86]
ATM	0.8–0.86	0.32–1.0	Pennington et al[36], Cancer Genome Atlas Research Network[38], Minion et al[83]
BRIP1	0.9–4.0	0.32–1.0	Walsh et al[8], Pennington et al[36], Cancer Genome Atlas Research Network[38], Ramus et al[87]
CHEK2	0.4–5.0	0.32–1.0	Walsh et al[8], Pennington et al[36], Cancer Genome Atlas Research Network[38], Minion et al[83]
FANCA	—	0.5	Kristeleit et al[86]
FANCI	—	0.5	Kristeleit et al[86]
NBN	0.2–1.0	0.63–1.0	Walsh et al[8], Pennington et al[36], Cancer Genome Atlas Research Network[38], Candido-dos-Reis[71], Minion et al[83]
PALB2	0.2–2.0	0.63	Walsh et al[8], Pennington et al[36], Cancer Genome Atlas Research Network[38], Ramus et al[87]

Non-BRCA HRRm was not predictive of improved PFS, regardless of gene panel in 1L OC(PAOLA-1)



bev=bevacizumab; CI=confidence interval; HR=hazard ratio; HRRm=homologous recombination repair gene mutation; NC=not calculable; PFS=progression-free survival

Pujade-Lauraine E, et al. Presented at the SGO Annual Meeting 2021; 19–25 March; Virtual

HRR gene panel作為卵巢癌治療生物標記存在的挑戰

對於BRCA1/2突變，已經建立很好的HRD和PARP抑制劑敏感性的相關性[1]

現存問題：對於BRCA 1/2wt的卵巢癌患者，還須檢測其他哪些HRR相關基因，哪些基因的突變可高度預測HRD?

考慮因素:

- 突變頻率
- HRR功能影響程度
- 如何分析臨床意義不明的變異(VUS)

1. The Cancer Genome Atlas Research Network Nature 2011; 474:609-615

Approach 2: Function of HRR

Function of HRR

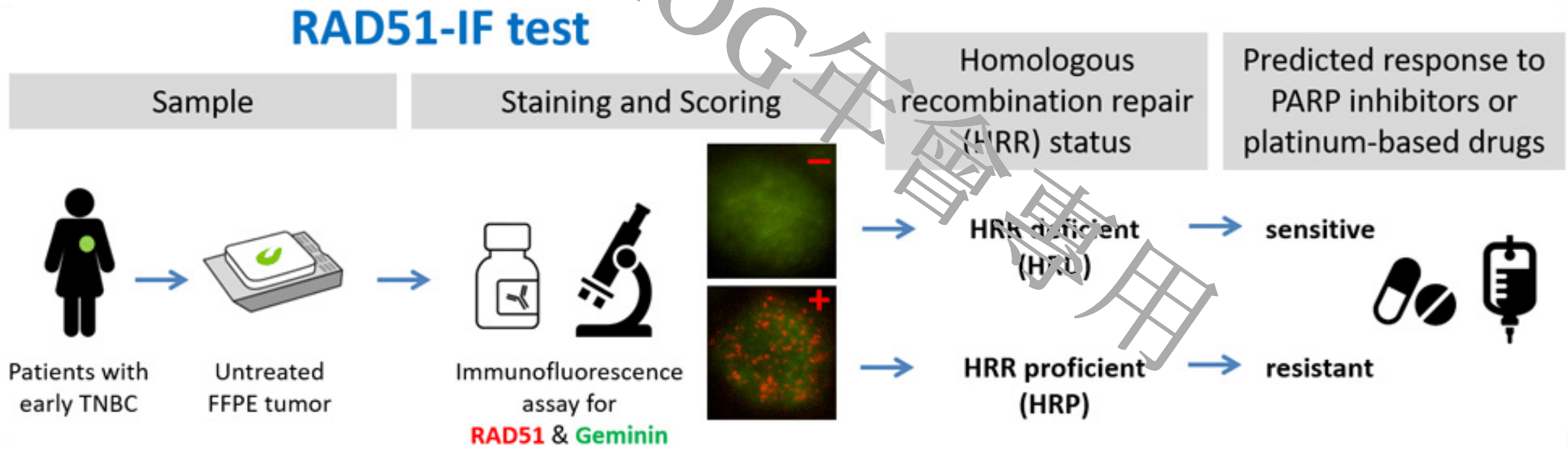
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO > Oncology News

THE RAD51-IF TEST IS FEASIBLE FOR ASSESSMENT OF THE FUNCTIONAL STATUS OF HOMOLOGOUS RECOMBINATION REPAIR IN TNBC TUMOURS

Results from two studies support further development to incorporate RAD51 testing in clinical decision making

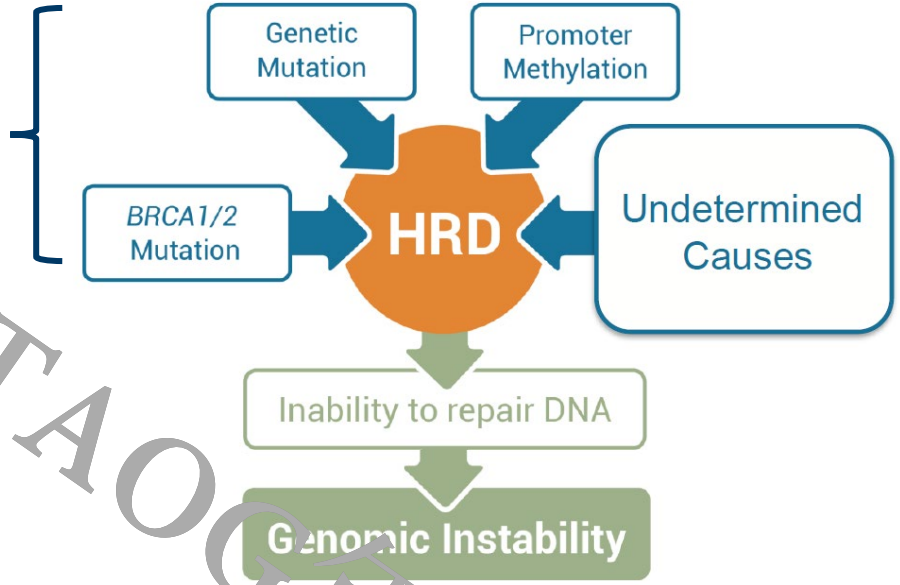
Date: 07 May 2021
Topics: Breast cancer; Translational research



1. Serra Elizalde V, Llop-Guevara A, Pearson A, et al. Detection of homologous recombination repair deficiency (HRD) in treatment-naive early triple negative breast cancer (TNBC) by RAD51 foci and comparison with DNA-based tests.
2. Llop-Guevara A, Vladimirova V, Schneeweiss A, et al. Association of RAD51 with Homologous Recombination Deficiency (HRD) and clinical outcomes in untreated triple-negative breast cancer (TNBC): analysis of the GeparSixto randomized clinical trial.

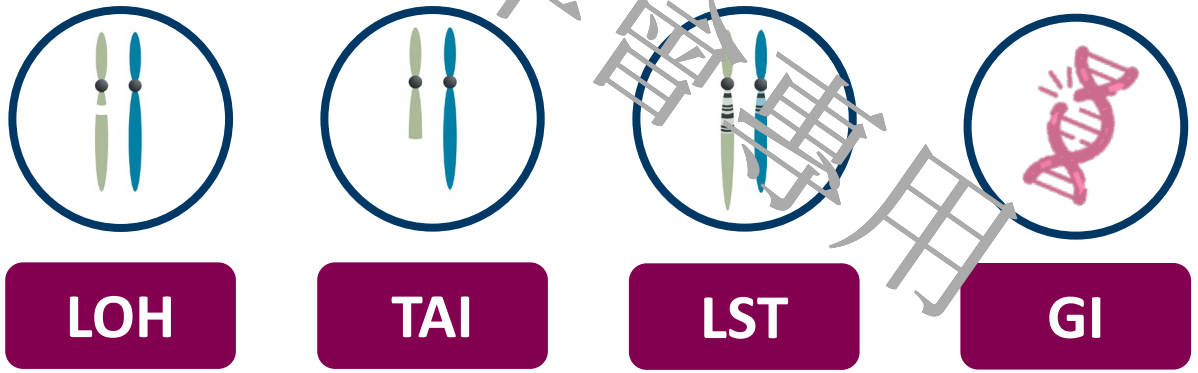
Approach 3: Effect of HRD

Effect of HRD



Genomic Scar

Methods to detect genetic scar



LOH: Loss of heterozygosity ; TAI: Telomeric allelic imbalance ; LST: Large-scale state transitions ; GI: Genomic integrity

1. Serra Elizalde V, Llop-Guevara A, Pearson A, et al. Detection of homologous recombination repair deficiency (HRD) in treatment-naive early triple negative breast cancer (TNBC) by RAD51 foci and comparison with DNA-based tests.

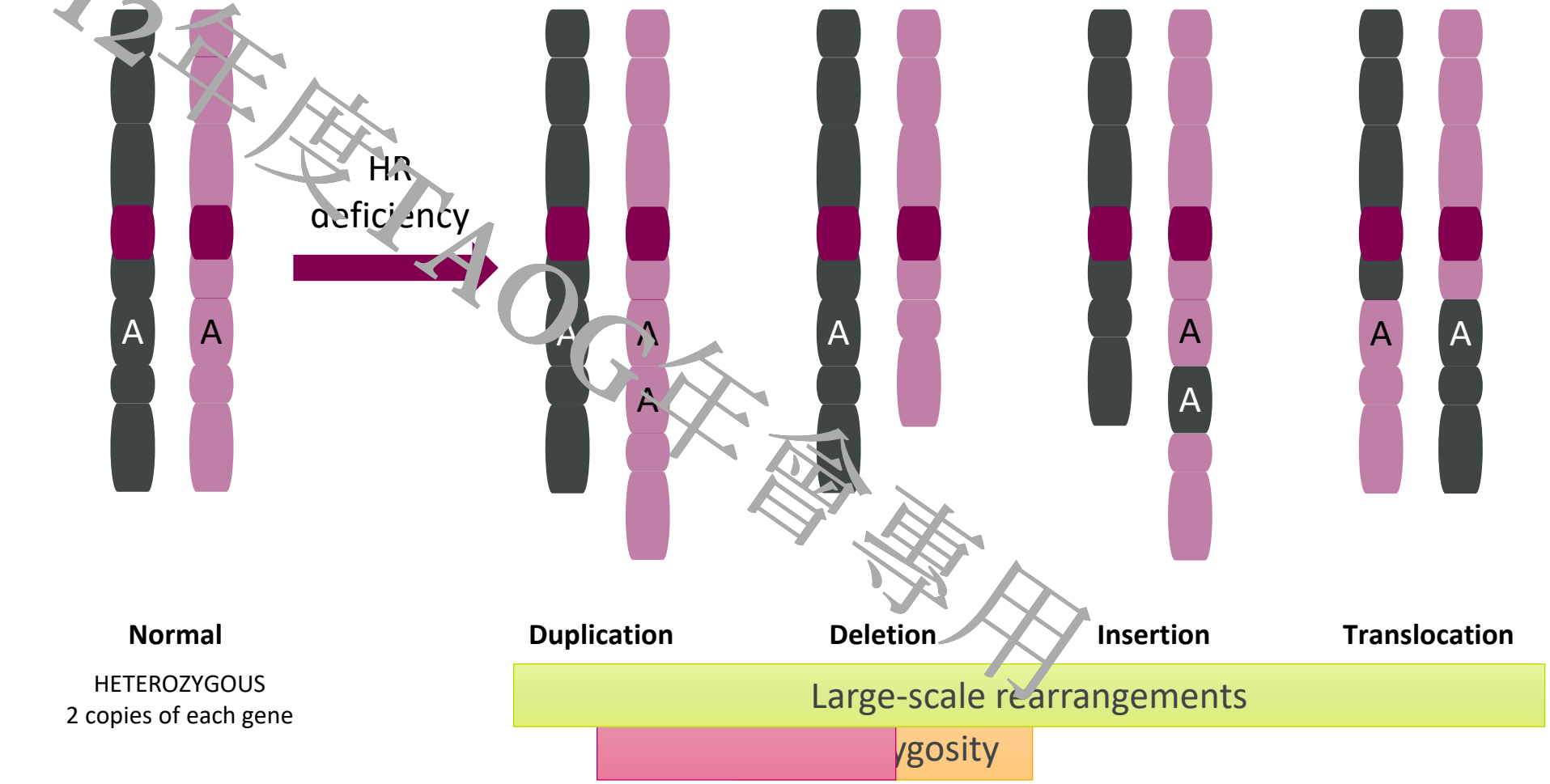
2. Llop-Guevara A, Vladimirova V, Schneeweiss A, et al. Association of RAD51 with Homologous Recombination Deficiency (HRD) and clinical outcomes in untreated triple-negative breast cancer (TNBC): analysis of the GeparSixto randomized clinical trial.

The effects of HR deficiency are seen as accumulation of DNA damage

Loss of HR

Error-prone repair of DNA

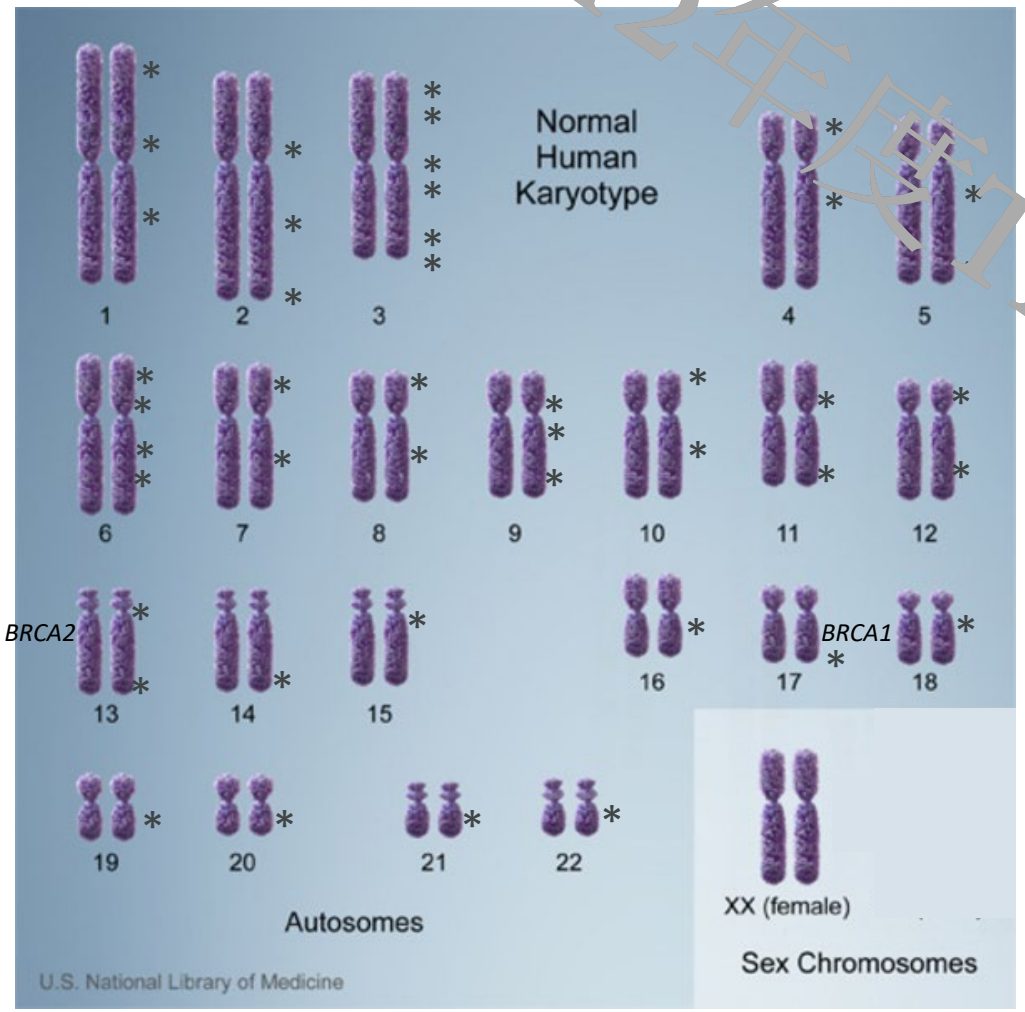
Accumulation of characteristic DNA damage



Rodgers and McVey. J Cell Physiol. 2016; 231(1): 15-24

How do we detect “LOH” & calculate the score

LOH detection by **genome-wide** sequencing
(usually done by NGS)



Credit: U.S. National Library of Medicine; modified from MedlinePlus

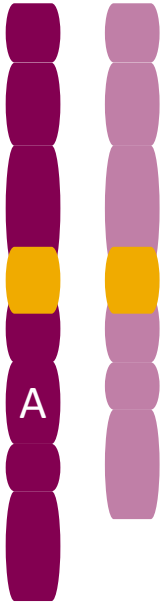
1. Selected meaningful SNP
2. Algorithm

→ **HRD Score**

- All patented
- The lab’s own knowhow

Genomic Instability and SNP Testing

- Genomic instability (e.g. LoH) tests are NOT based on gene panels, but are specialized tests that require pan-genome SNP coverage



Loss of Heterozygosity

Design principles for SNP selection:

1. SNPs are evenly distributed across the genome.
2. SNPs should be from the regions that are unique in the genome.
   - Low complexity region will complicate the analysis.
3. SNPs have good population allele frequency (GMAF); in other words a significant proportion of the selected SNPs should be heterozygous

The SNP density can determine the minimum size of LoH segment detected.
A sparse SNP assay can miss LOH segments

Abkevich V et al. Br J Cancer 2012 ;107: 1776–1782; Swisher EM et. al. Lancet Oncol. 2017 Jan;18(1):75-87.

Primary Maintenance Trials

	SOLO-1 (N = 391)	PRIMA/ENGOT-OV26 (N = 733)	PRIME (N = 384)	ATHENA-Mono (N = 538)	PAOLA-1/ENGOT-OV25 (N = 806)	VELIA/GOG-3005 (N = 1140)
Treatment arms	**Olaparib** vs placebo	**Niraparib** vs placebo	**Niraparib (IBW)** vs placebo	**Rucaparib** vs placebo	**Olaparib** + bevacizumab vs Placebo + bevacizumab	**Veliparib** + CP → **veliparib** **Veliparib** + CP → placebo Placebo + CP → placebo
HRD testing	N/A	Myriad myChoice® HRD score ≥42	**BGI Genomics** HRD score	**Foundation One CDx** HRD LOH > 16%	myChoice® HRD Plus HRD score ≥42	myChoice® HRD CDx **HRD score ≥33**

Taiwan

1. Myriad myChoice® (LOH+TAI+LST)
2. Fundation one CDx (LOH)
3. ACT HRD (LOH)

4. SOPHiA HRD→ not SNP based

LOH: Presence of a single allele

TAI: A discrepancy in the 1:1 allele ratio at the end of the chromosome (telomere)

LST: Transition points between regions of abnormal and normal DNA or between two different regions of abnormality

The HRD Testing Platforms

Myriad myChoice® CDx

The test content

1. Tumor BRCA1/2

2. HRD Score

Score content

- LOH (54,091 SNPs)
- TAI
- LST
- Patented Algorithm

HRD score: 0~100
HRD positive: ≥42 (PAOLA-1 trial)
LOH platform: NGS (illumine, HiSeq)

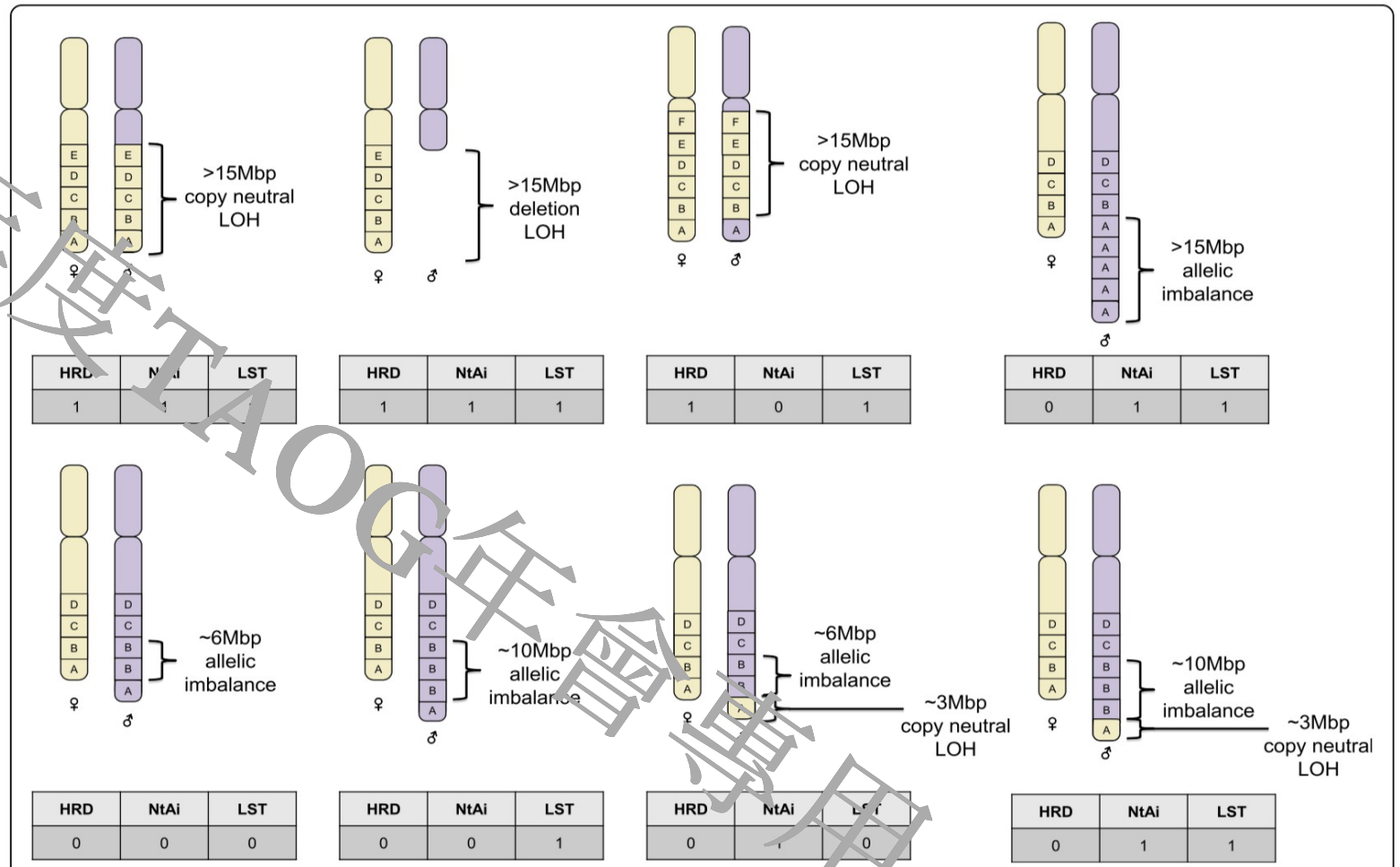
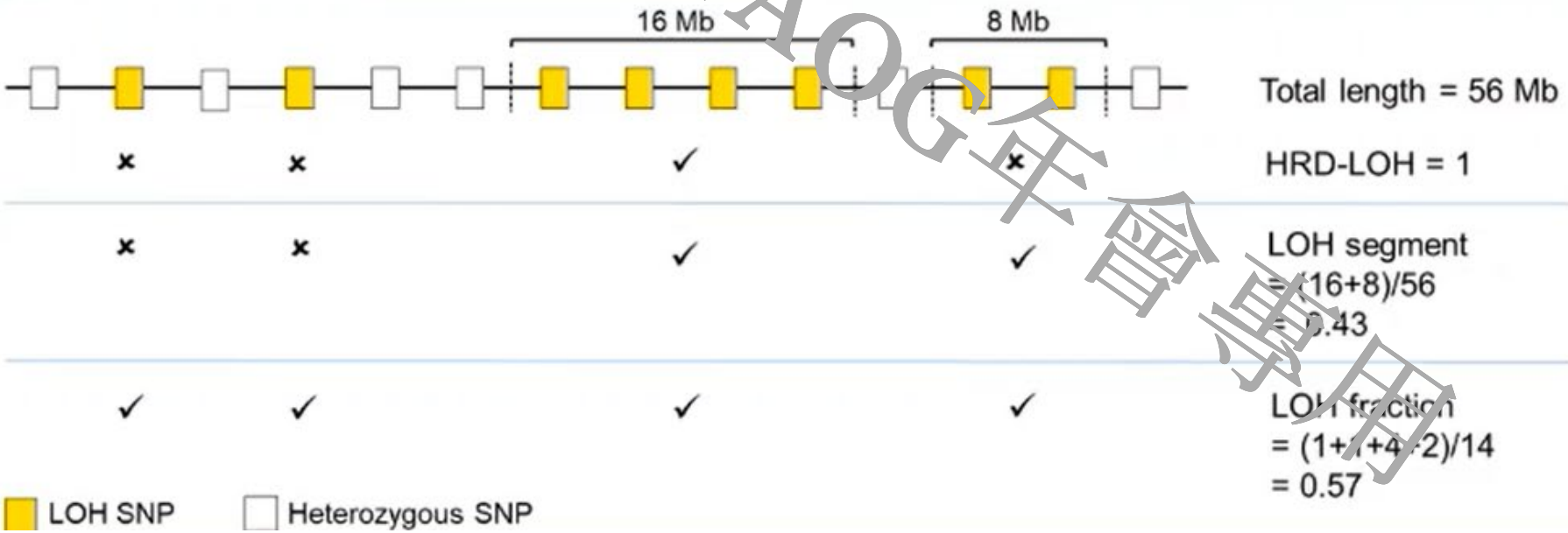


Figure 2 Scoring by genomic scars of homologous recombination deficiency and drug response. Eight examples of various forms of structural copy number aberrations and rearrangements are given, whereby each box, lettered A to F, represents a genomic segment of approximately 3 Mbp in length. Below the chromosomes, the three genomic scars - homologous recombination defect (HRD), telomeric allelic imbalance score (NtAi), and large-scale transition (LST) - are listed along with the respective integer count for the scar (0 = not seen, 1 = detected once). LOH, loss of heterozygosity.

1. https:// www.Myriad.com. ; 2. https://www.foundationmedicine.com/test/foundationone-cdx ; 3. https://www.actgenomics.com/patients_product.php?id=5 ; .4. FoundationFocus $CDx_{BRCA\ LOH}$ Technical Information., https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160018S001c.pdf. Accessed August 28, 2018. 5. Morgan, Robert D., et al. "PARP inhibitors in platinum-sensitive high-grade serous ovarian cancer." *Cancer chemotherapy and pharmacology* 81.4 (2018): 647-658.
LOH: Loss of heterozygosity ; TAI: Telomeric allelic imbalance ; LST: Large-scale state transitions ; TMB: Tumor mutation burden ; MSI: Microsatellite instability

Methodology comparison: LOH score

Panel	LOH score	LOH counting methodology
Company 1	HRD-LOH	continuous LOH events > 15 Mb
Company 2	Genome-wide LOH (segment)	$\text{LOH} = \frac{\text{Total length of continuous LOH SNPs}}{\text{Total length of HET SNPs}}$
ACTHRD™	Genome-wide LOH (fraction)	$\text{LOH} = \frac{\text{Total number of LOH SNPs}}{\text{Total number of HET SNPs}}$



From ACT

Myraid:54901SNP

Fundation one:3500SNP

ACTHRD: 9000SNP

ACTHRD™ Performance

HRD Status		Comparator Assay			
		True Positive	True Negative	Invalid	Total
ACTHRD™	Positive	23	1	0	24
	Negative	0	10	0	10
	Invalid	1	[illegible]	1	2
	Total	24	11	[illegible]	36
Agreement Including Valid Results Only	PPA [95% CI]	100.00% [85.69%, 10[illegible].00%]			
	NPA [95% CI]	90.91% [62.26%, 99.53%]			
	OPA [95% CI]	97.06% [85.08%, 99.85%]			
Agreement Including Invalid Results	PPA [95% CI]	95.83% [79.76%, 99.79%]			
	NPA [95% CI]	90.91% [62.26%, 99.53%]			
	OPA [95% CI]	94.29% [81.39%, 98.42%]			

Definition of Positive with FDA-approved test:

BRCA1/2 mutation

or

GIS score ≥ 42

Definition of Positive with ACTHRD™:

BRCA1/2 mutation

or

LOH score ≥ 0.4

Effect of HRD

Effect of HRD

Two different HRD test methodologies: (1) LOH, TAI and LST (2) GI

Myriad myChoice® CDx

FoundationOne® CDx

ACT HRD

LOH

TAI

LST

HRD

Genomic Instability

SOPHiA GENETICS

Genomic Integrity (GI)

SOPHiA HRD DDM Solution: a cost-effective & easy to adapt application for HRD detection

- Enables users to independently conduct HRD testing in their own laboratories
- Combines the sequencing of HRR genes & measures genomic integrity in a single assay
- Easy to implement in your lab with strong expert support & SOPHiA Set Up Program
- SOPHiA DDM Platform analytics & HRD status assessment in a user-friendly & intuitive interface

Targeted sequencing

Somatic & germline mutations in 28 HRR genes incl. *BRCA1/2*

Low-pass whole genome sequencing

High coverage of low-pass data into algorithm-trained feature extraction

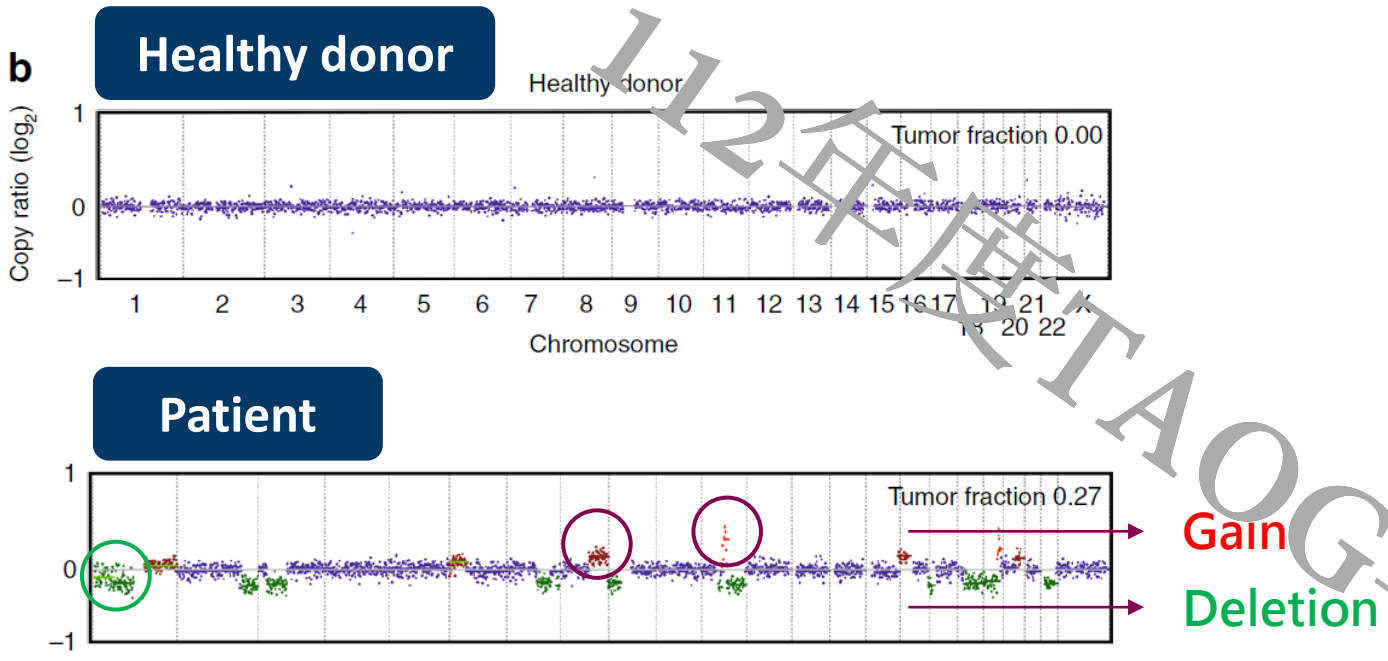
Deep learning

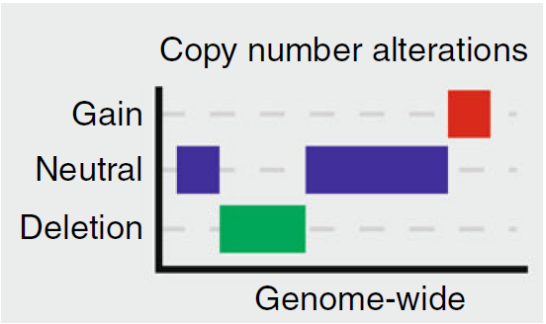
Convolutional neuronal networks reveal genomic integrity

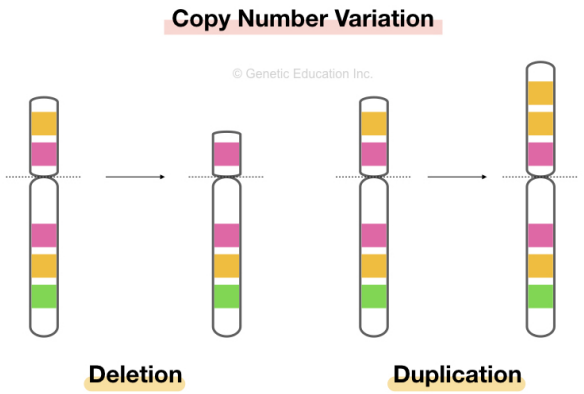
SOPHiA DDM Platform

Sample-to-report workflow with high quality analytical & interpretation capabilities

Low-pass 全基因定序 (Low-pass WGS)







- 若 copy number 有 gain or deletion，表示發生 CNV (Copy Number Variation)，DNA修復功能可能有問題
- 已普遍應用於產前基因檢測 (NIPS)
- 高通量、檢測速度快、範圍廣

Adalsteinsson, V.A., et al., Nat Commun, 2017. 8(1): p. 1324

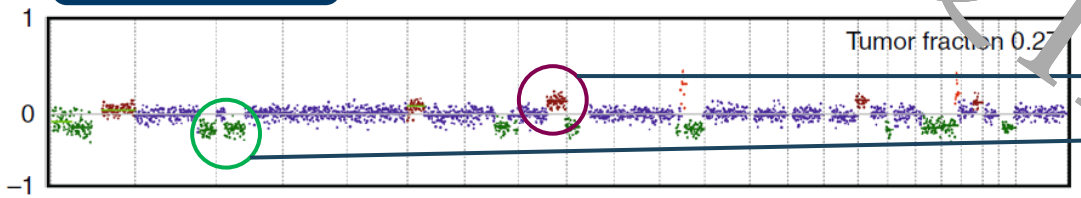
WGS: whole genome sequence, 全基因定序

如何尋找Low-pass 全基因定序圖像化特徵？跟誰做對比？

AI 深度學習 Model

示意圖：

HRD +



Adalsteinsson, V.A., et al., Nat Commun, 2017. 8(1): p. 1324

圖像特徵

利用經 Myriad 檢測為 HRD+ (超過3000人)之 low-pass WGS 圖形，來讓 AI 做深度學習：

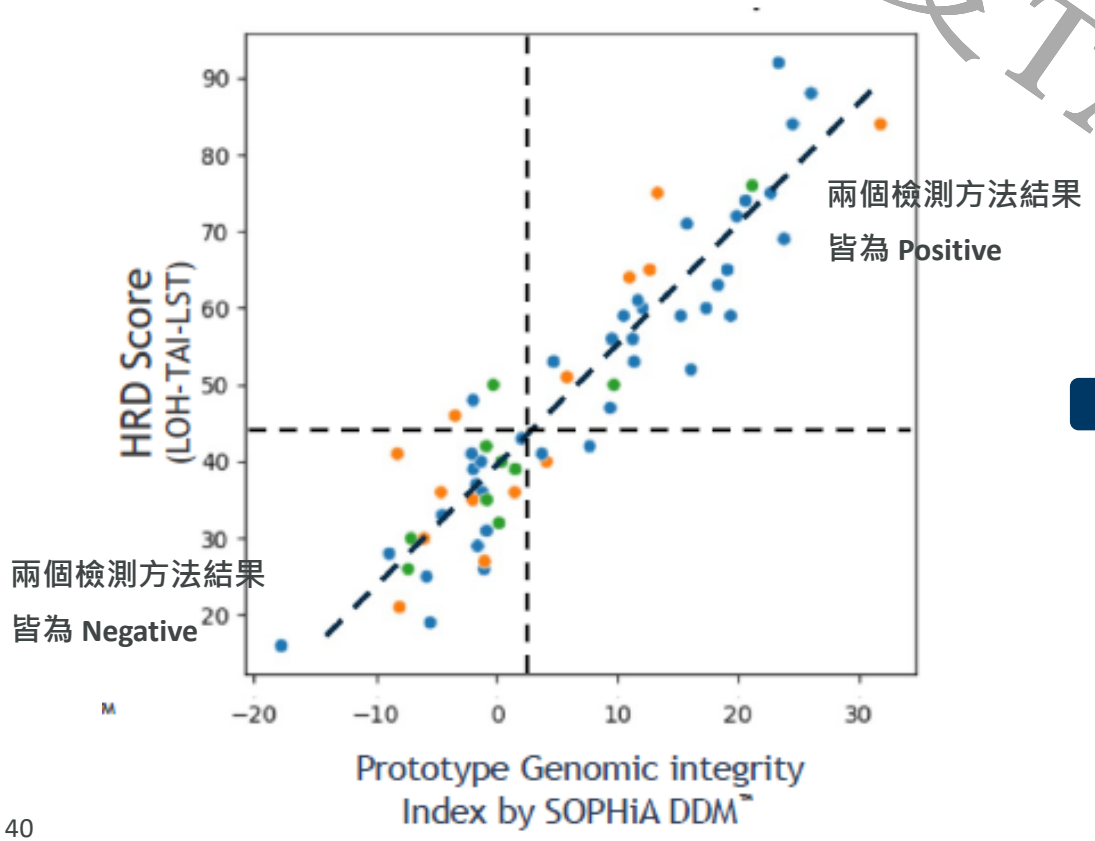
從Myriad-confirmed HRD+ 病人的 low-pass WGS 圖像，找出 HRD+ 在 low-pass WGS 中的圖像特徵，進而學習分析判斷 HRD status

Concordance Data

SOPHiA GENETICS

Preliminary Data (Internal Study)

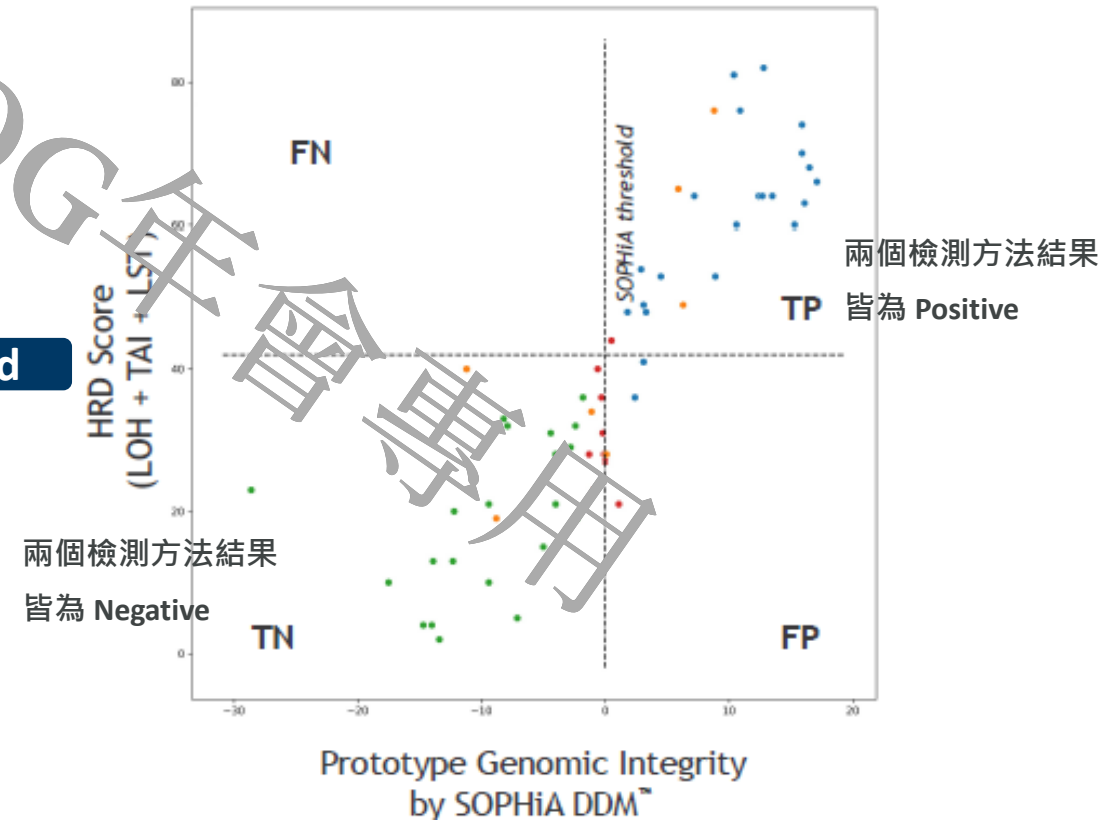
The SOPHiA solution was assessed using **62** high-grade serous Ovarian Cancer samples



External Lab (will have peer to peer review publish)

- **53 samples** passed SOPHiA DDM™ sample QA
- Observed **concordance with HRD score** (LOH + TAI + LST) : **94%**

Myriad



Poster #579P

A multicenter evaluation of a low-pass whole genome sequencing-based solution for homologous recombination deficiency detection

A. Buisson*[1], P. Saintigny[1], E. Pujade-Lauraine[2], C. Montoto-Grillot[2], D. Vacirca[3], M. Barberis[3], N. Colombo[3], A. Harlé[4], P. Gilson[4], C. Roma[5], F. Bergantino[5], P. Harter[6], S. Pignata[7], A. Gonzalez-Martin[8], C. Schauer[9], K. Fujiwara[10], I. Vergote[11], T. Jakobi Noettrup[12], P.A. Just[13], I. Ray-Coquard[14]

[1] Département de Biopathologie, Centre Léon Bérard; Lyon, France. [2] Arcagy Ginaco; Paris, France. [3] European Institute of Oncology; Milan, Italy. [4] Département de Biopathologie, Institut de Cancérologie de Lorraine, CNRS UMR 7039 CRAN, Université de Lorraine; Nancy, France. [5] Istituto Nazionale Tumori-IRCCS-Fondazione G. Pascale, I-80131; Naples, Italy. [6] Kliniken Essen Mitte; Essen, Germany. [7] Department of Urology and Gynecology, Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, and Multicenter Italian Trials in Ovarian Cancer and Gynecologic Malignancies (MITO); Naples, Italy. [8] Clínica Universidad de Navarra, Madrid, Program in Solid Tumors, CIMA, Pamplona, and GEICO; Spain. [9] Hospital Barmherzige Brüder; Graz, Austria. [10] Saitama Medical University International Medical Center; Japan. [11] University Hospital Leuven, Leuven Cancer Institute; Leuven, Belgium, European Union. [12] Copenhagen University Hospital; Denmark. [13] Cochin, APHP; Paris, France. [14] Centre Léon Berard and University Claude Bernard Lyon I; Lyon, France.

*Corresponding author: Dr. Adrien Buisson. **Adrien.BUISSON@lyon.unicancer.fr**

ESMO 2022

SOPHiA HRD, CE-IVD approved

Ovarian cancer, multicenter real-world performance evaluation

5 independent clinical laboratories

Decentralized analysis:

No significant difference in OPA was observed between SOPHiA GENETICS™ or by 4 independent labs

HRD status concordance rate: 93.7 % ; kappa value: 0.88

GI Status		Myriad myChoice® CDx		
		Positive	**Negative**	**Rejected**
SOPHiA DDM™ Dx HRD Solution	**Positive**	66	2	0
	Negative	6	63	1
	Neg. with an FN risk	1	5	1
	Inconclusive	0	3	1
	Rejected	0	0	0

Sample number: **149**

PPA	90.4 %
NPA	97.1 %
OPA (Concordance rate)	**93.7 %**

PPA: Positive percent agreement，陽性的一致性

NPA: Negative percent agreement，陰性的一致性

OPA: Overall percent agreement

A. Buisson et al., ESMO 2022 (VOLUME 33, SUPPLEMENT 7, S811-S812,)
DOI:https://doi.org/10.1016/j.annonc.2022.07.707

A deep learning solution for detection of homologous recombination deficiency in ovarian cancer using low pass whole-genome sequencing: Evaluation of the analytical performance.

SOPHiA HRD

- Ovarian cancer
- 4 independent clinical laboratories
- Reproducibility: 100% (n=4)
- HRD status concordance rate: 94.5 % ; kappa value: 0.871

Confusion matrix of comparison between Myriad myChoice CDx and GII results.

		SOPHiA GENETICS GII status	
		Positive	Negative
Myriad myChoice CDx status	Positive	66	6
	Negative	3	64

Sample number: **139**

PPA	91.7 %
NPA	95.5 %
OPA (Concordance rate)	**94.5 %**

PPA: Positive percent agreement，陽性的一致性
NPA: Negative percent agreement，陰性的一致性
OPA: Overall percent agreement

J Clin Oncol 40, 2022 (suppl 16; abstr e17599)
https://doi.org/10.1200/JCO.2022.40.16_suppl.e17599

Real world data

HRD testing platforms overview

Myriad myChoice® CDx

The test content

1. Tumor BRCA1/2

2. HRD Score

Score content

- LOH (54,091 SNPs)
- TAI
- LST
- Patented Algorithm

HRD score: 0~100
HRD positive: ≥42 (PAOLA-1 trial)
LOH platform: NGS (illumina, HiSeq)

FoundationOne® CDx

The test content

1. Tumor BRCA1/2

2. HRD Score (LOH)

3. 322 genes

4. TMB

5. MSI

Score content

- LOH (in coding exons from 309 cancer-related genes)

LOH platform: NGS (illumina, HiSeq)

Other Solutions

1 LDT (Laboratory Development Test)

ACT Genomics (Taiwan)

GC Genome (Korea)

2 Kit Solution

SOPHiA GENETICS | Amoy | illumina | Thermo Fisher | Roche

1. https:// www.Myriad.com. ; 2. https://www.foundationmedicine.com/test/foundationone-cdx ; 3. https://www.actgenomics.com/patients_product.php?id=5 ; .4. FoundationFocus CDx$_{BRCA\ LOH}$ Technical Information., https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160018S001c.pdf. Accessed August 28, 2018. 5. Morgan, Robert D., et al. "PARP inhibitors in platinum-sensitive high-grade serous ovarian cancer." *Cancer chemotherapy and pharmacology* 81.4 (2018): 647-658.
LOH: Loss of heterozygosity ; TAI: Telomeric allelic imbalance ; LST: Large-scale state transitions ; TMB: Tumor mutation burden ; MSI: Microsatellite instability

Current available data about SOPHiA in Taiwan

50.33% of Patients with Ovarian Cancer Tested **HRD Positive** by SOPHiA Genetics HRD Kit, in accordance with Published Data

(from 14/02/2022 to 21/12/2022)

	Cancer types			
	Ovarian cancer	Fallopian tube cancer	Peritoneal cancer	Total
Total cases, n	457	24	31	512
HRD positive, n (%)	230 (50.33)	18 (75.00)	16 (51.61)	264 (51.56)
BRCA mutated, n (%)	89 (19.47)	6 (25.00)	6 (19.35)	101 (19.73)
GII positive BRCA wild-type, n (%)	141 (30.85)	12 (50.00)	10 (32.26)	163 (31.84)
HRD negative, n (%)	227 (49.67)	6 (25.00)	15 (48.39)	248 (48.44)

Data provided by SOFIVA.

SOFIVA GENOMICS

50.35% of Patients with Ovarian Cancer Tested HRD Positive by SOPHiA Genetics HRD Kit, in accordance with Published Data

(from 02/2022 to 06/2023 CareHRD Project)

	Cancer types			
	Ovarian cancer	Fallopian tube cancer	Peritoneal cancer	Total
Total cases, n	723	40	43	806
HRD positive, n (%)	364 (50.35)	25 (62.50)	25 (58.14)	414 (51.36)
BRCA mutated, n (%)	133 (18.40)	11 (27.50)	7 (16.28)	151 (18.73)
GII positive BRCA wild-type, n (%)	231 (31.95)	14 (35.00)	18 (41.86)	263 (32.63)
HRD negative, n (%)	359 (49.65)	15 (37.50)	18 (41.86)	392 (48.64)

Data provided by SOFIVA.

European Journal of Cancer 188 (2023) 131–139

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

PARP inhibitor predictive value of the Leuven HRD test compared with Myriad MyChoice CDx PLUS HRD on 468 ovarian cancer patients from the PAOLA-1/ENGOT-ov25 trial

Highlights

••Results of ENGOT HRD initiative on 468 shared FFPE samples of the PAOLA-1 trial.

••Academic Leuven HRD test shows comparable results with Myriad MyChoice HRD test.

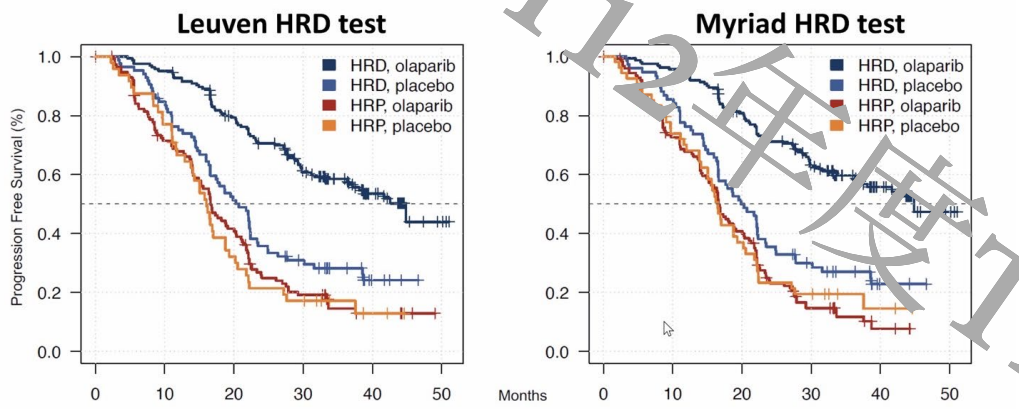
••Leuven HRD test confirms the impact of olaparib on PFS and OS in the HRD+ patients.

	Positive percent agreement	Negative percent agreement	Overall percent agreement
BRCA analysis	95%	99.6%	98%
HRD GIS scoring	88%	86%	87%

- 468 / 806 PAOLA-1 patients were included in the analysis
- Overall HRD status was 54% positive for Leuven vs 52% for MyChoice CDx Plus
- Unknown HRD status was 11% for Leuven vs 9% for MyChoice CDx Plus
- Both tests' BRCA analysis was highly correlated (95% PPA, 99.6% NPA)
- **HRD GIS scoring was less correlated (88% PPA, 86% NPA)**

Leuven HRD test vs. Myriad (from PAOLA-1 trial)

HRD status versus PFS in PAOLA-1 (n=468) → **HRD+ (包含 BRCAm)** **差異不大的原因是否為受到 BRCAm 干擾所致？**



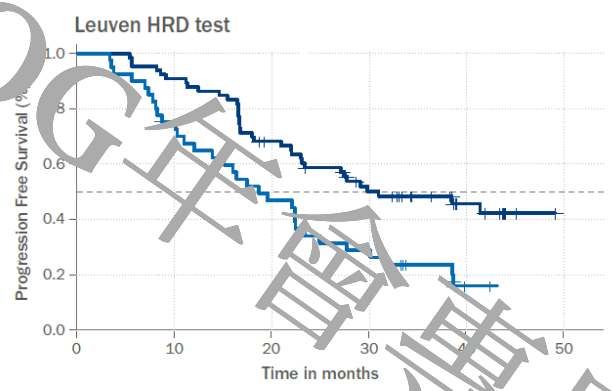
HRD = Homologous Recombination Deficient = HRD status positive (all, including BRCA)
HRP = Homologous Recombination Proficient = HRD status negative (BRCAwt/unknown)

	Positive percent agreement	Negative percent agreement	Overall percent agreement
BRCA analysis	95%	99.6%	98%
HRD GIS scoring	88%	86%	87%

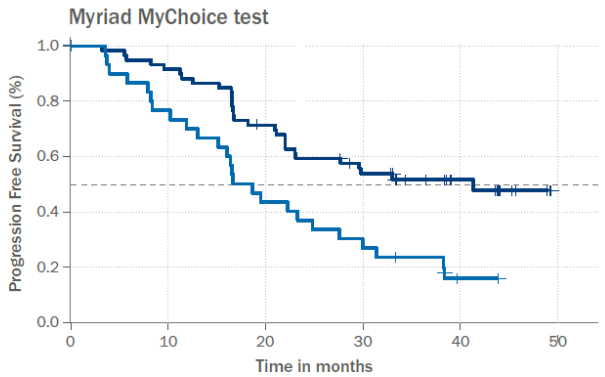
- 468 / 806 PAOLA-1 patients were included in the analysis
- Overall HRD status was 54% positive for Leuven vs 52% for MyChoice CDx Plus
- Unknown HRD status was 11% for Leuven vs 9% for MyChoice CDx Plus
- Both tests' BRCA analysis was highly correlated (95% PPA, 99.6% NPA)
- **HRD GIS scoring was less correlated (88% PPA, 86% NPA)**

若只看 HRD+, BRCAwt 的族群，PFS 還是有差異 (差10.6 個月)

HRD status positive (only BRCAwt)



	HRD, olaparib	HRD, placebo
n	66	41
Events	35 (53%)	32 (78%)
Median PFS	31.1	18.6
PFS at 24 months	59%	34%
HR (95% CI)	0.455 (0.281–0.738)	



	HRD, olaparib	HRD, placebo
n	60	31
Events	29 (48%)	25 (81%)
Median PFS	41.7	17.6
PFS at 24 months	59%	36%
HR (95% CI)	0.407 (0.237–0.698)	

Liselore L. et al., Gynecologic Oncology, Volume 166, Supplement 1, 2022, Pages S51-S52, ESGO congres 2022, Poster
Myriad myChoice

Blinded-assessment of SOPHiA DDM™ Dx HRD Solution to evaluate olaparib maintenance treatment efficacy in ovarian cancer patients from the GINECO/ENGOT PAOLA-1 trial

A. Buisson[1*], P. Saintigny[2], P. Constantoulakis[3], K. Oikonomaki[3], S. Samara[3], P. Harter[4], S. Pignata[5], A. Gonzalez-Martin[6], C. Schauer[7], K. Fujiwara[8], I. Vergote[9], N. Colombo[10], E. Pujade-Lauraine[11], I. Treilleux[12], I. Ray-Coquard[13], on behalf of the PAOLA Study Group and ENGOT Intergroup Consortium.

[1] Département de Biopathologie, Centre Léon Bérard; Lyon, France; [2] University of Lyon, Université Claude Bernard Lyon 1, INSERM 1052, CNRS 5286, Centre Léon Bérard, Centre de Recherche en Cancérologie de Lyon, Lyon, France; Department of Medical Oncology, Centre Léon Bérard, Lyon, France; [3] Genotypos Science Labs, Athens, Greece; [4] Kliniken Essen Mitte, Essen, Germany; [5] Department of Urology and Gynecology, Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, and Multicenter Italian Trials in Ovarian Cancer and Gynecologic Malignancies (MITO), Naples, Italy; [6] Cancer Center Clínica Universidad de Navarra, Madrid, Program in Solid Tumors, CIMA, Pamplona, and GEICO; Spain; [7] Hospital Barmherzige Brüder; Graz, Austria; [8] Saitama Medical University International Medical Center, Japan; [9] University Hospital Leuven, Leuven Cancer Institute, Leuven, Belgium, European Union; [10] European Institute of Oncology, Milan and MANGO, Italy; [11] Association de Recherche Cancers Gynécologiques (ARCAGY), Paris, France; [12] Centre de Recherche en Cancérologie de Lyon, Centre Léon Bérard, Université de Lyon, Lyon, France; [13] Centre Léon Berard, and University Claude Bernard Lyon I, Lyon and Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO), France.

*Corresponding author: Dr. Adrien Buisson. Adrien.BUISSON@lyon.unicancer.fr

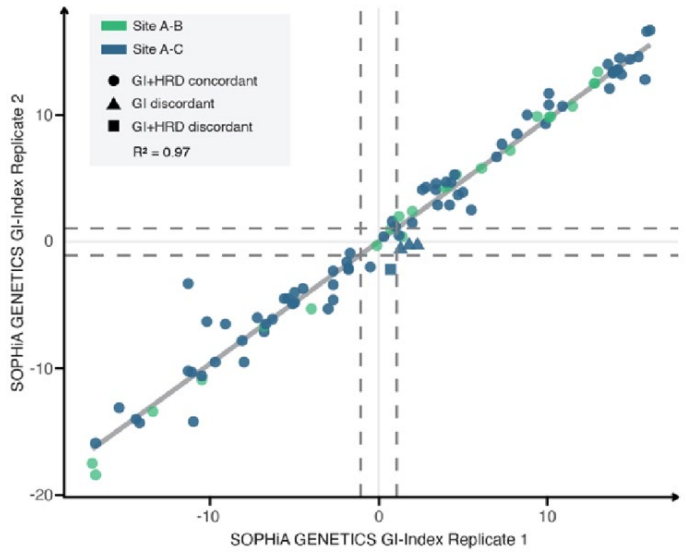
Poster #5588

359 ovarian cancer samples from **PAOLA-1 trial**

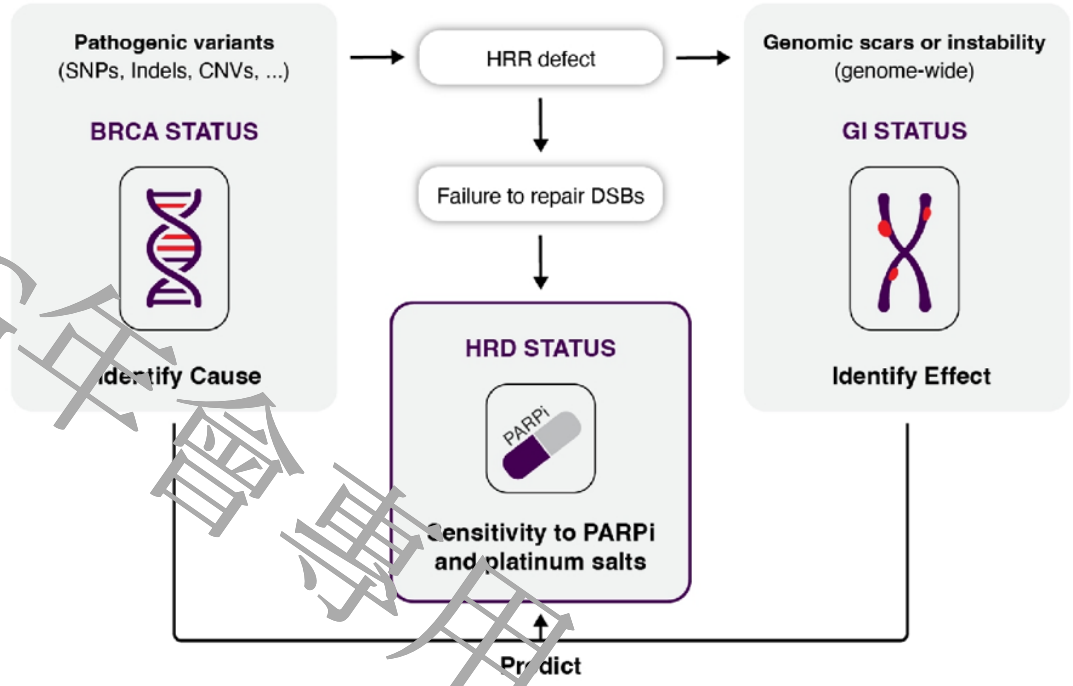
3 independent clinical laboratories

High reproducibility, R^2 = 0.97 (n= 97)

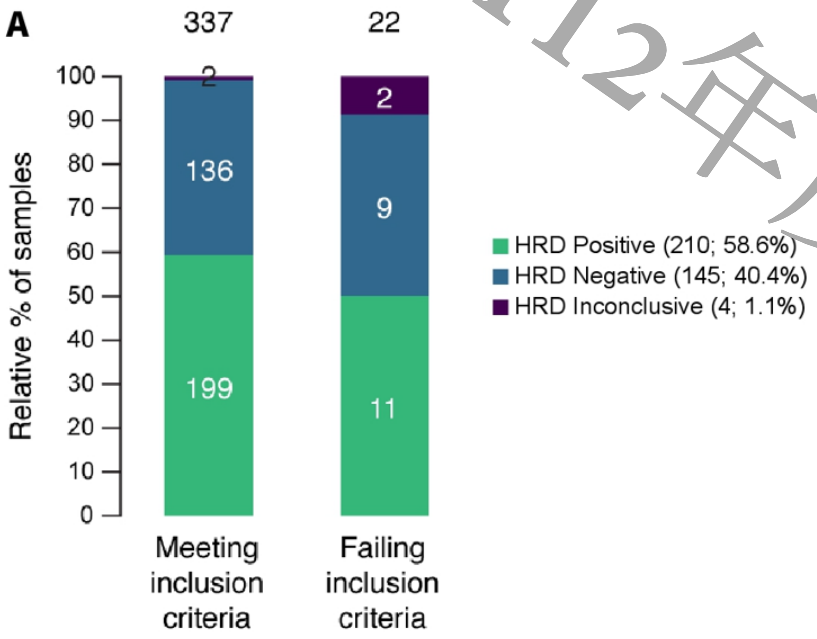
HRD status concordance rate: **98.1 %** (SOPHiA vs. Myriad)

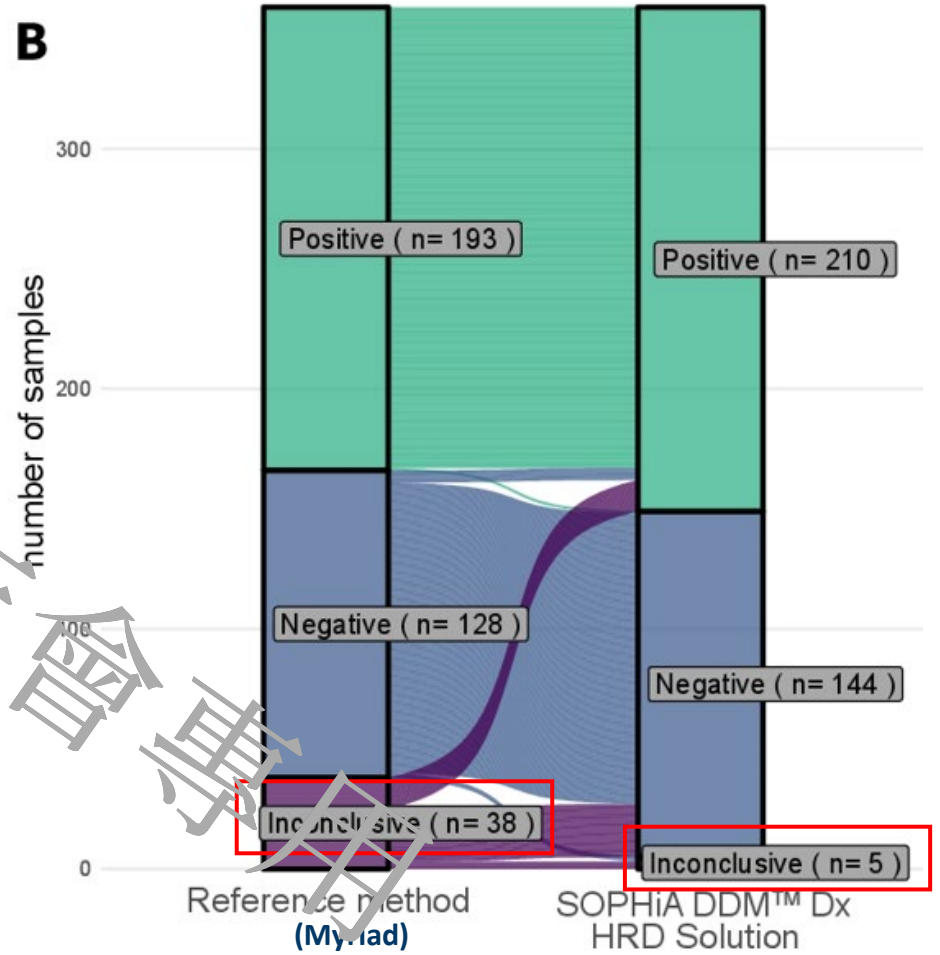


High reproducibility in 3 different labs



The overall rejection rate of SOPHiA HRD solution was low (1.1 %)



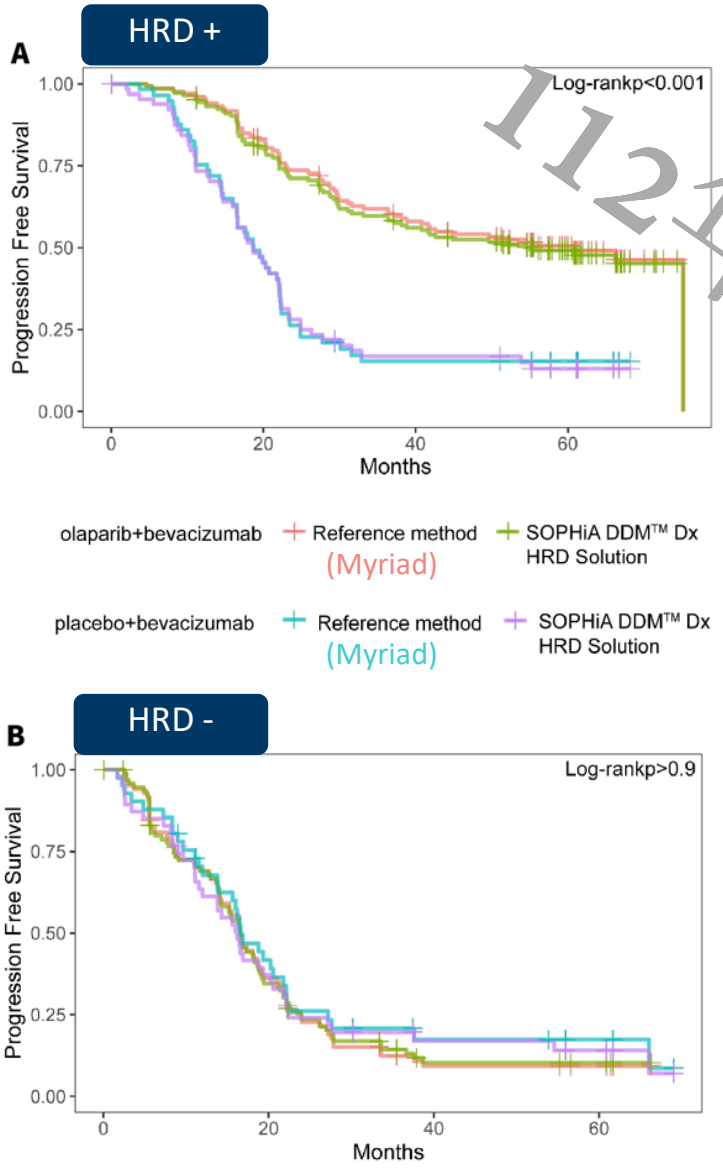


- 6 % (22/359) of samples did not meet manufacture's QC criteria due to low sample input and low tumor content

- The HRD status of 91 % of those (20/22) could still be estimated by SOPHiA HRD solution

Less inconclusive result compared to Myriad

Clinical relevance of SOPHiA HRD solution in PAOLA-1



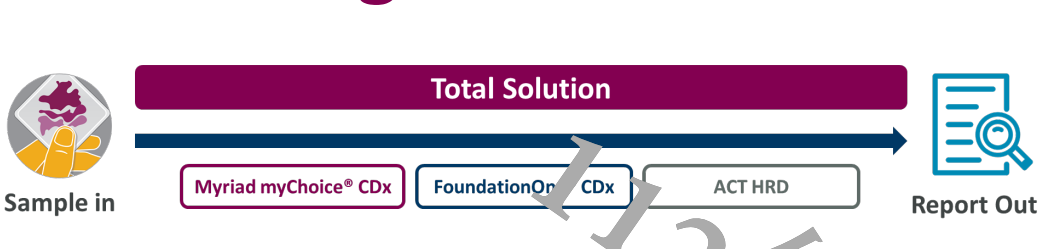
Both two HRD testing exhibit highly similar PFS and overall survival (OS, data not shown)

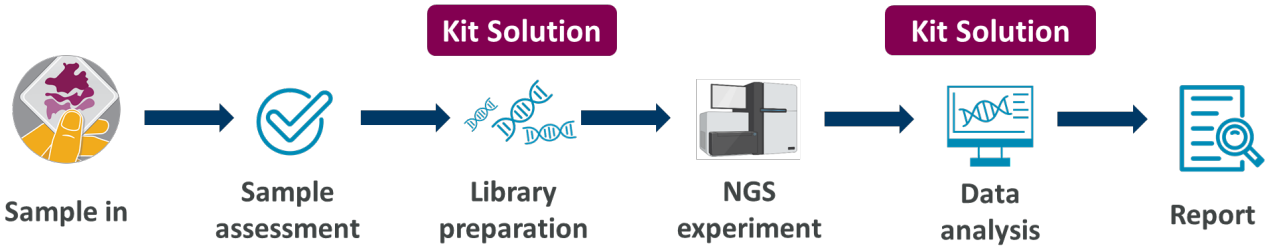
	SOPHiA DDM™ Dx HRD Solution	Reference method (Myriad)
PFS in patients with HRD-positive status		
Number of samples	210	193
Hazard ratio (95% CI)	**0.32 (0.22 – 0.45)**	**0.30 (0.21 – 0.44)**
Median survival time, months (95% CI)		
Placebo + bevacizumab	18.7 (16.6 – 22.1)	18.7 (16.5 – 22.1)
Olaparib + bevacizumab	55.7 (37.2 – NA)	60.7 (40.8 – NA)
PFS in patients with HRD-negative status		
Number of samples	145	128
Hazard ratio (95% CI)	**1.03 (0.71 – 1.52)**	**1.16 (0.77 – 1.75)**
Median survival time, months (95% CI)		
Placebo + bevacizumab	16.2 (12.0 – 21.8)	16.6 (13.9 – 22.1)
Olaparib + bevacizumab	16.6 (14.3 – 18.9)	16.6 (14.3–19.1)

Summary

- The retrospective results from PAOLA-1 trial, 359 ovarian cancer sample were analysis by SOPHiA HRD solution
- SOPHiA HRD solution had highly HRD concordance rate (98.1 %) with the Myriad method
- Ovarian cancer with HRD positive status, assessed by either SOPHiA and Myriad method, had an equal benefit from Olaparib maintenance therapy
- Low rejection rate (1.1 %) in SOPHiA HRD solution
- High reproducibility (R^2 = 0.97) in 3 different labs showing the value of the decentralized SOPHiA HRD solution

HRD testing overview in Taiwan





	Trial Central Lab	Trial Central Lab	Local LDT Solution	Kit Solution				
Company	Myriad	Foundation	ACT Genomics	Illumina	Amoy	SOPHiA	Roche (FMI)	Thermo Fisher
IVD	IVD/CE-IVD	IVD/CE-IVD	N/A	RUO	CE-IVD	CE-IVD	RUO	N/A
Availability In Taiwan	in market	in market	in market	2022.Q	in market	in market	In market	2023 Q1
Validation/ Concordance	100% Global trial use: PAOLA-1 PRIMA VELIA NOVA….	100% Global trial use: ARIEL3 ATHENA	95% (N=36) (concordance vs Myriad)	94 % (N=197) (concordance vs Myriad) ESGO 2021 96 % (N=198) ASCO 2022	82% (N=98) (concordance vs Myriad) ESGO 2021 87.8% (N=49) ASCO 2022	94.5% (N=139) (concordance vs Myriad) ASCO 2022 93.7% (N=159) ESMO 2022 98.1% (N=359, PAOLA-1 sample) ASCO 2023	N/A	N/A

Take home message and Thanks