HOMOLOGOUS RECOMBINATION DEFICIENCY (HRD) TESTING IN OVARIAN CANCER: AIMING TO INCREASE THE CLINICAL UTILITY OF PARP INHIBITORS

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THE CROWN PRINCESS MARY CANCER CENTRE, WESTMEAD

SYDNEY WEST TRANSLATIONAL CANCER RESEARCH CENTRE

NSW GOVERNMENT Health Western Sydney Local Health District

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ANZ GOG 2019
ANNUAL SCIENTIFIC MEETING
SYDNEY 20 – 23 MARCH 2019

Faculty Disclosure

	No, nothing to disclose

	Honoraria/ Expenses	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership / Equity Position*	*Employee*	*Other (please specify)*

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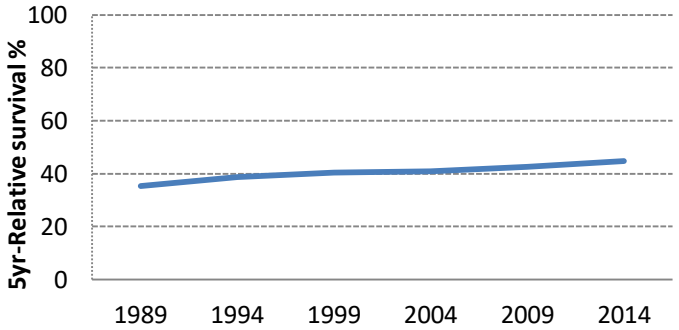
	No

Epithelial ovarian cancer

- Most often advanced, widespread disease at diagnosis
- Treatment is largely the same (surgery + carboplatin/paclitaxel chemotherapy)
- Most women (~70%) are initially responsive to treatment, but development of acquired resistance is common
- Survival is slowly increasing, but remains <45%



Source: AIHW & NBOCC Ovarian Cancer in Australia 2014

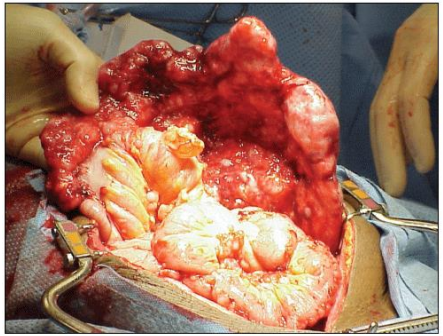
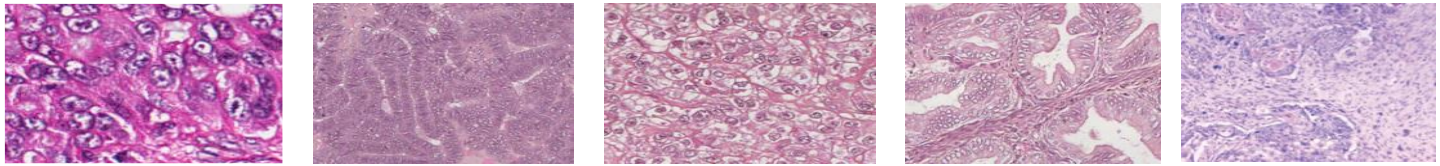


Figure 1: Omental Caking—a common finding in the two-thirds of ovarian cancer patients who present with advanced disease.

Ovarian cancer subtypes and potential targeted therapy

Histology



Serous 70% | Endometrioid 10% | Clear Cell 7% | Mucinous 4% | Carcinosarcoma 3%

Mutations

Serous:
- *TP53*, *BRCA1*, *BRCA2*
- *KRAS*, *BRAF*, *NRAS*

Endometrioid:
- *ARID1A*
- *CTNNB1*
- *KRAS*
- *PIK3CA*
- *PTEN*

Clear Cell:
- *ARID1A*
- *PIK3CA*
- *PTEN*
- *PIK3R1*

Mucinous:
- *TP53*
- *KRAS*
- *ERBB2*^{amp}

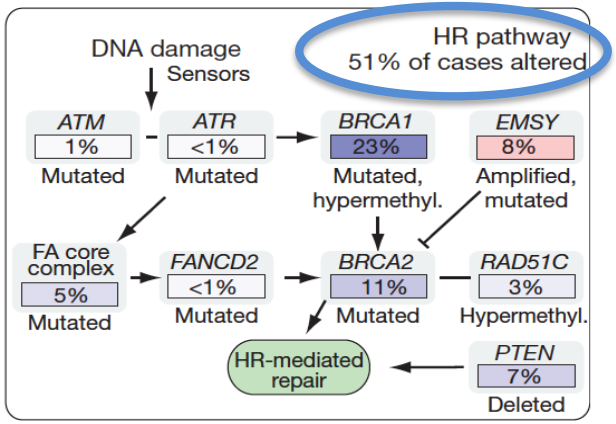
Carcinosarcoma:
- *ARID1A*
- *KRAS*
- *PIK3CA*
- *TP53*

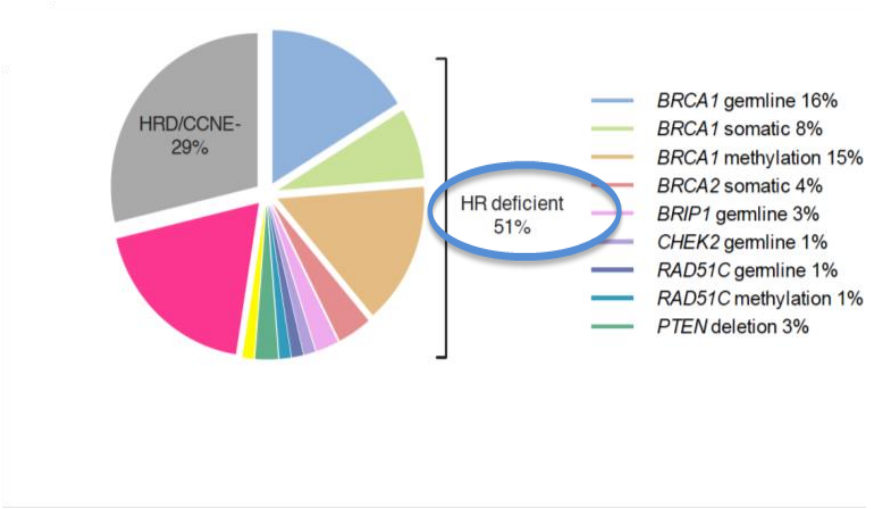
Low-grade serous, LGSC

High-grade serous, HGSC

Alterations in homologous recombination (HR) repair are common in HGSC

BRCA mutation and loss of functional *BRCA* activity leads to HR dysfunction in ~50% of high-grade serous ovarian cancer

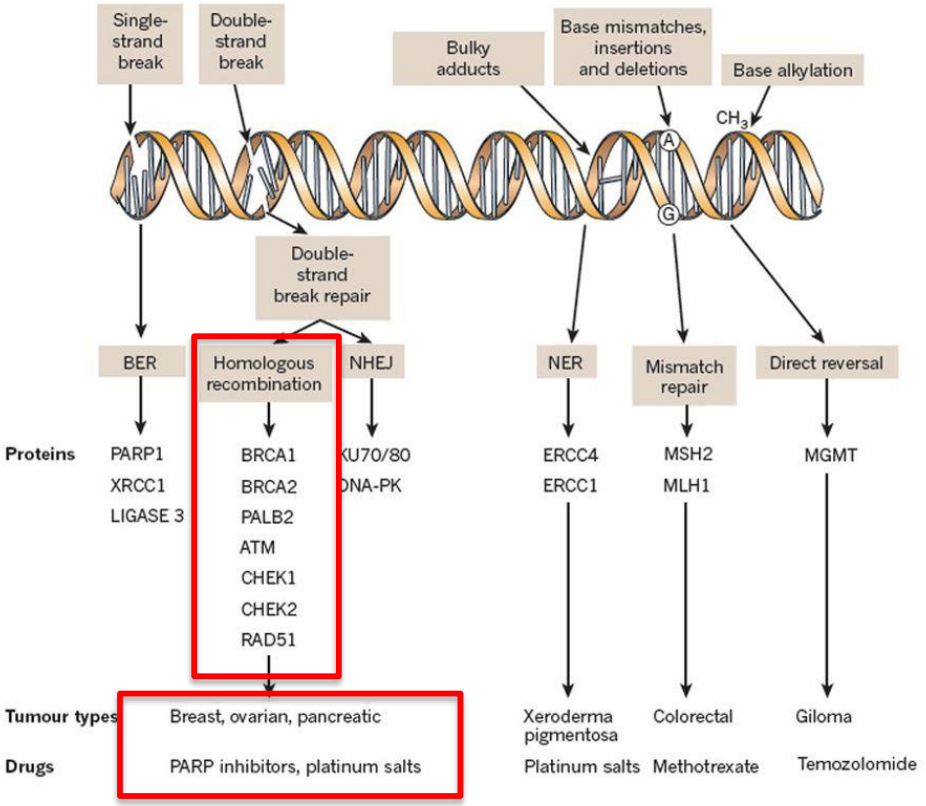




The Cancer Genome Atlas (TCGA) 2012 *Nature;* Ciriello et al., 2013 *Nat Genetics*

Whole genome sequencing: International Cancer Genome Consortium (ICGC) Bowtell, deFazio and Grimmond labs
Patch *et al*, Nature 2015; 521 (7553):489-94

Alterations in HR are associated with response to platinum chemotherapy and PARP inhibitors



Lord and Ashworth, Nature 2012, 481: 287-94

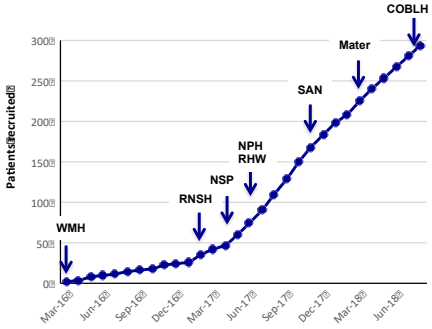
PARP inhibitors in HGSOC

PARP Inhibitor	Trial	Population group
Olaparib	SOLO2 [1]	→ *BRCA* mutated (all germline)
	SOLO1 [2]	→ *BRCA* mutated (99% germline)
	Study 19 [3]	→ *BRCA* mutated (germline or somatic, retrospective)
Niraparib	ENGOT-OV16/NOVA [4]	→ *BRCA* mutation (germline)
		HRD-positive, non-germline *BRCA* mutated
		non-germline *BRCA*-mutated
Rucaparib	ARIEL 3 [5]	→ *BRCA* mutated (germline)
		HRD assay positive (LOH)

[1] Pujade-Lauraine E, et al. Lancet Oncology 2017; 18:1274-84
[2] K Moore et al. N Engl J Med 2018;379:2495-2505
[3] Ledermman J et al. N Engl J Med 2012; 366:1382-92
[4] Mirza MR, et al. N Engl J Med 2016; 375: 2154-64
[5] Coleman RL, et al. Lancet 2017; 390:1949-61

INOVATe

Individualised Ovarian Cancer Treatment through Integration of Genomic Pathology into Multidisciplinary Care



March 2019

- 12 sites open
- > 350 eligible patients consented
- Next-gen sequencing, gene copy number, gene and protein expression
- Patients identified for marker-driven clinical trials

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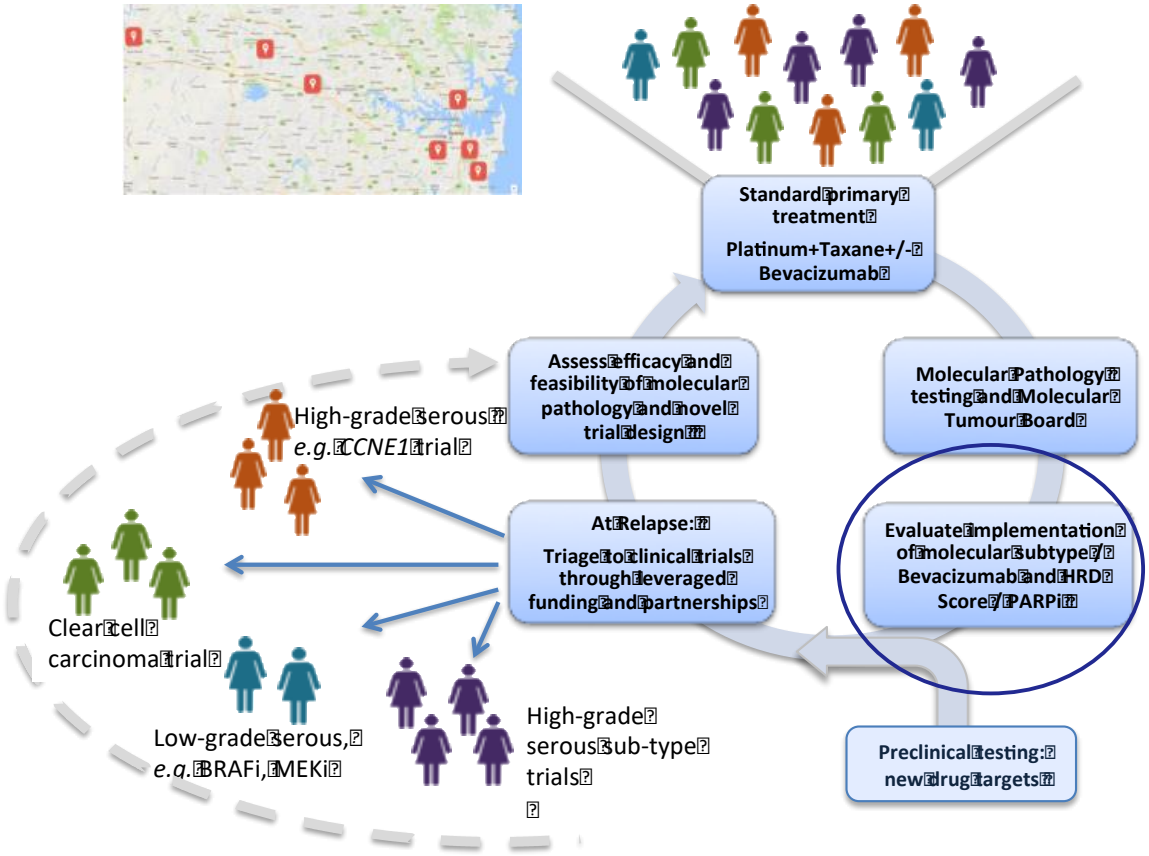
INOVATe

Individualised Ovarian Cancer Treatment through Integration of Genomic Pathology into Multidisciplinary Care

- Maximising PARPi use
- 2 approaches:
  - Tumour mutation testing
  - HRD score



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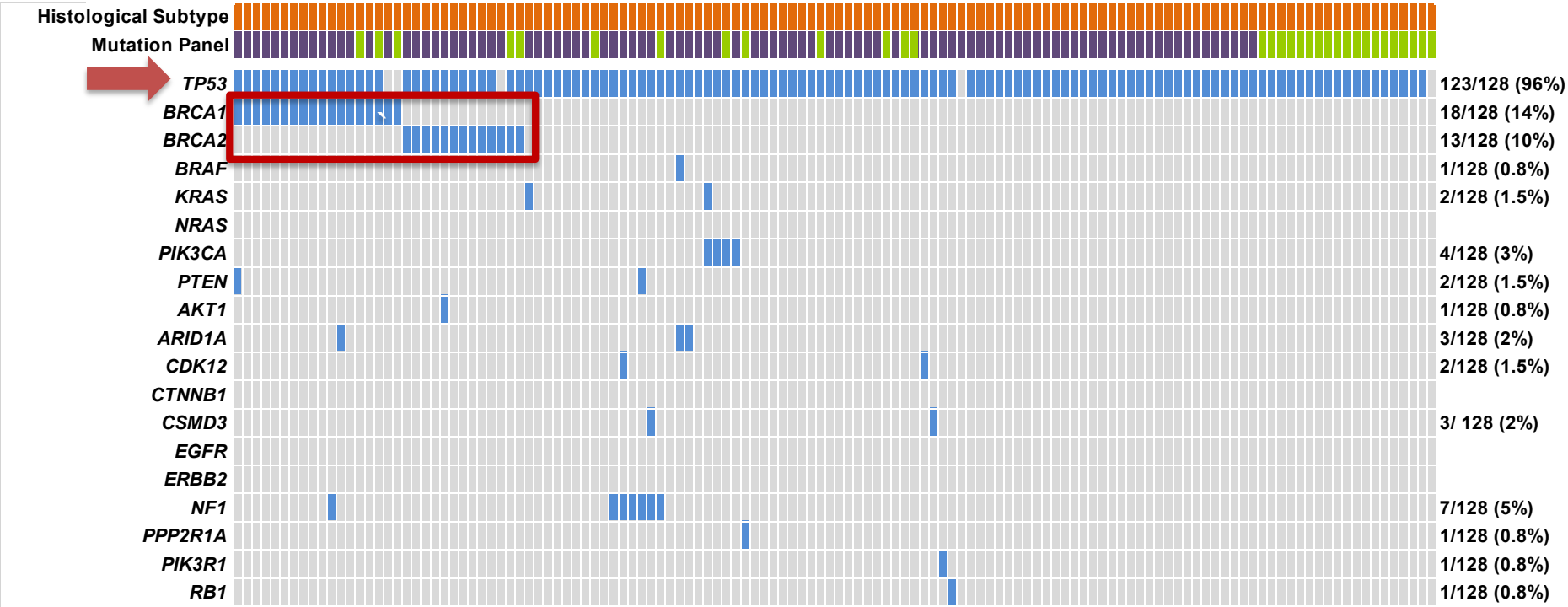
Mutation profile of HGSOC in INOVATe



- 128/199 (64%) tested are HGS
- Of the HGS: 31/128 (24%) were found to have *BRCA1/2* mutations in the tumour

Dashni Srirangan

BRCA1/2 mutation status

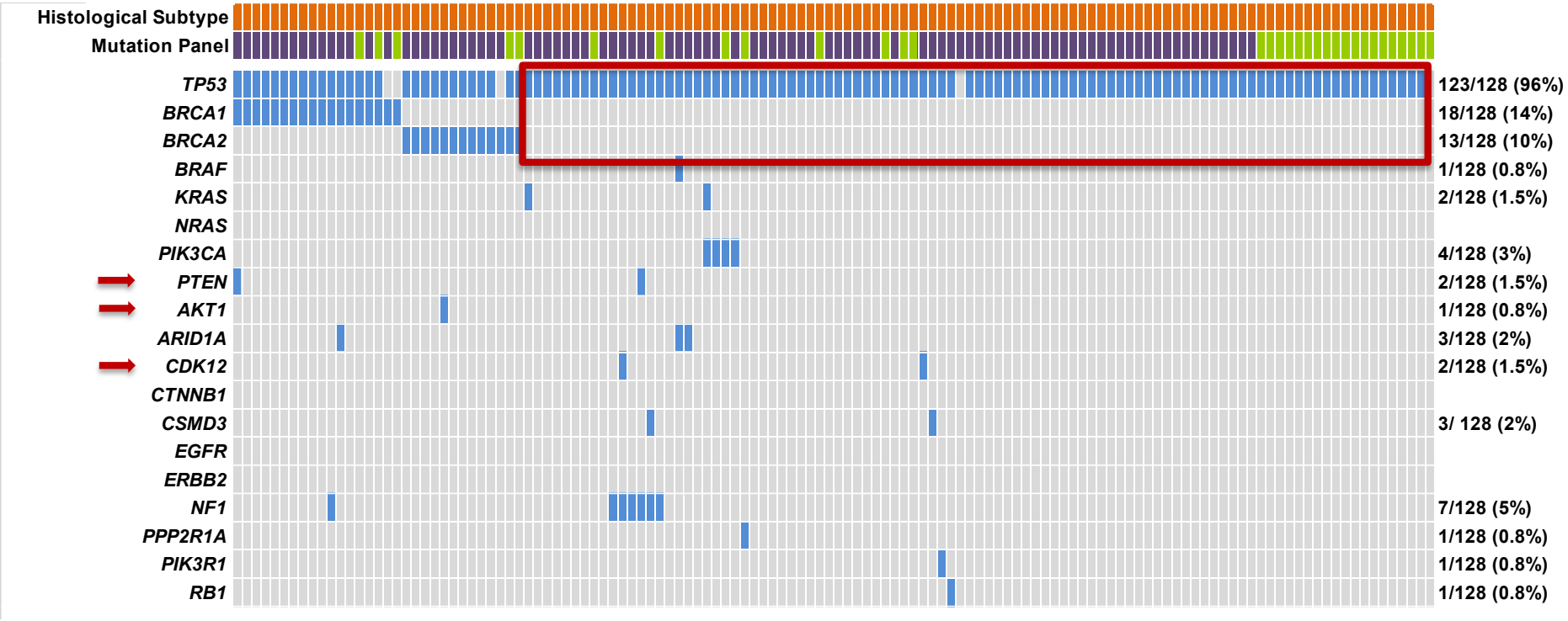
		INOVATe somatic testing	
	Pathogenic *BRCA1/2*^{mut}	Yes	No
Clinical germline testing	Yes	21	1
	No	7	36

BRCA1/2 mutation status reported by INOVATe somatic testing and clinical testing were highly concordant

- Somatic testing identified 21/22 (95.5%) germline *BRCA1/2* mutation
- However, in 1 case, a large duplication germline *BRCA1* variant was **NOT** detected by somatic panel testing

7 cases (10.8%) presumed somatic *BRCA1/2*^{mut} as they were **NOT** detected in germline testing

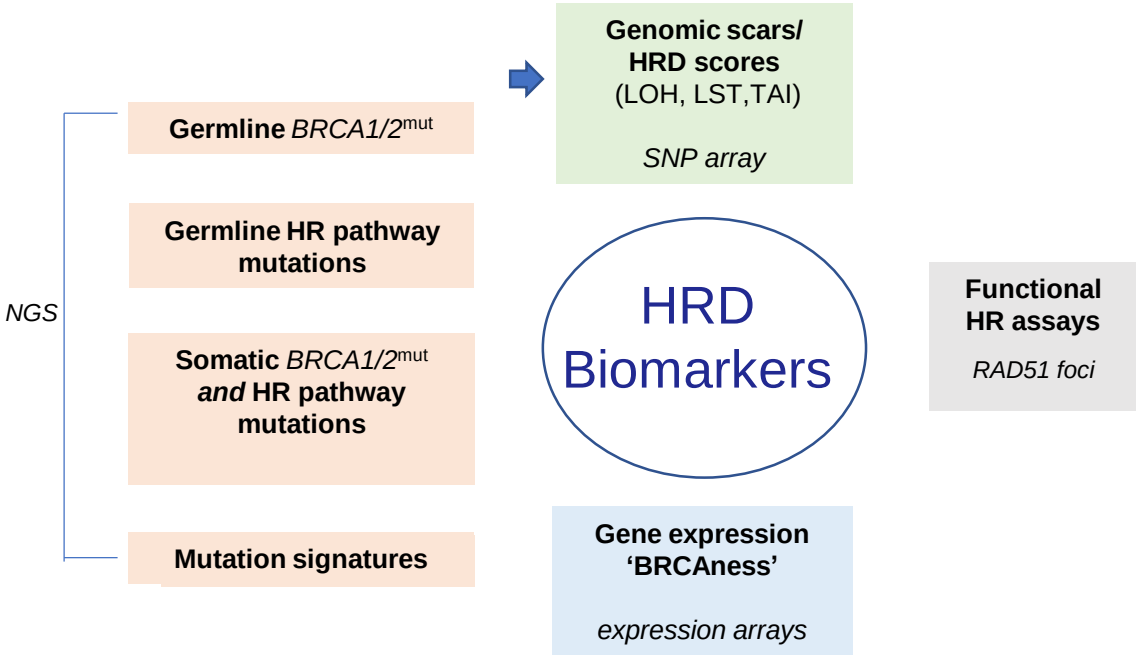
Mutation profile of HGSOC in INOVATe



- 75% HGS have no identified *BRCA1/2*^{mut}
- Mutation gene panel testing is limited to specific genes
  - frequency of non-*BRCA* mutations are low

Dashni Srirangan

Homologous Recombination Repair Deficiency (HRD) Biomarkers Assays

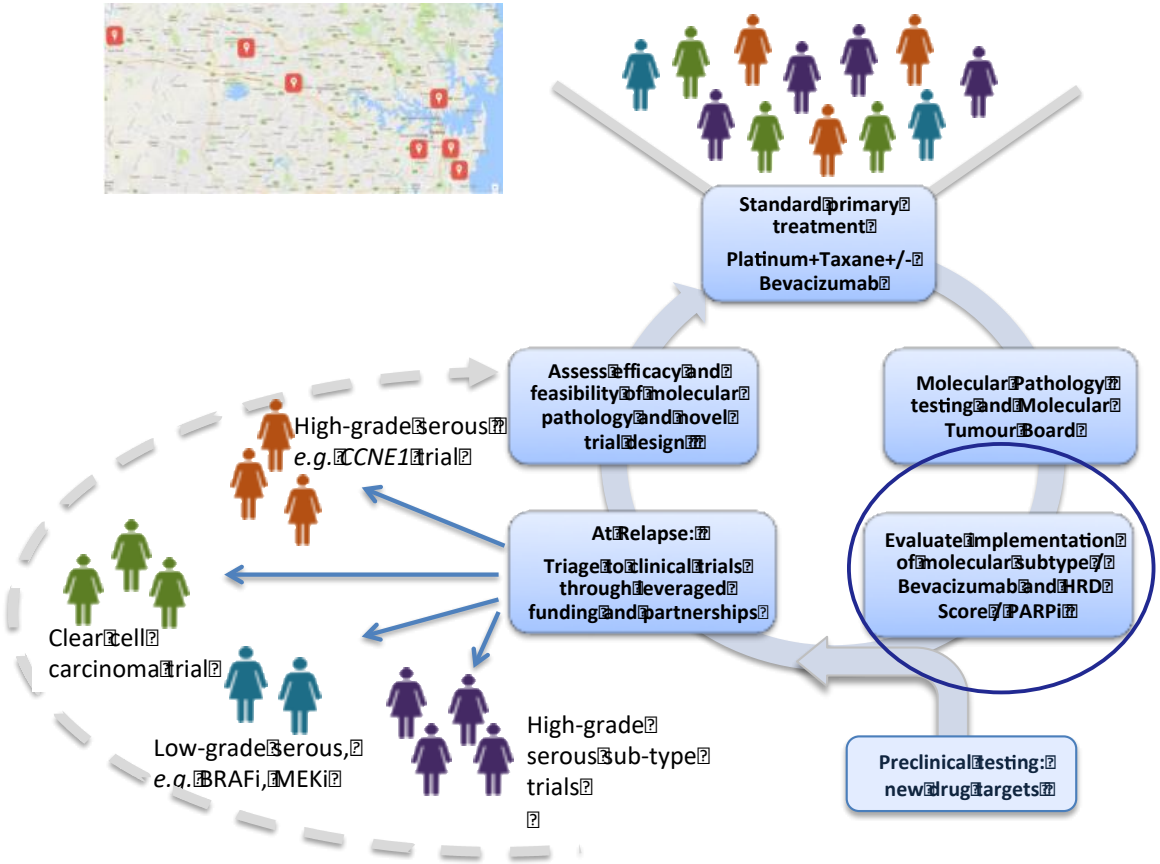


Adapted from Breast Cancer Research and Treatment (2018) 171:21-31

INOVATe

Individualised Ovarian Cancer Treatment through Integration of Genomic Pathology into Multidisciplinary Care

Evaluate implementation of HRD score to predict response to carboplatin and PARPi



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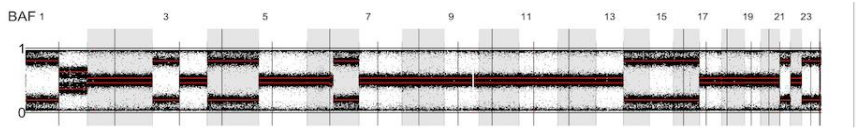
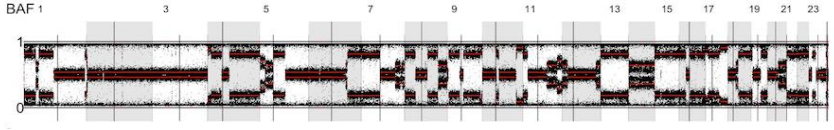
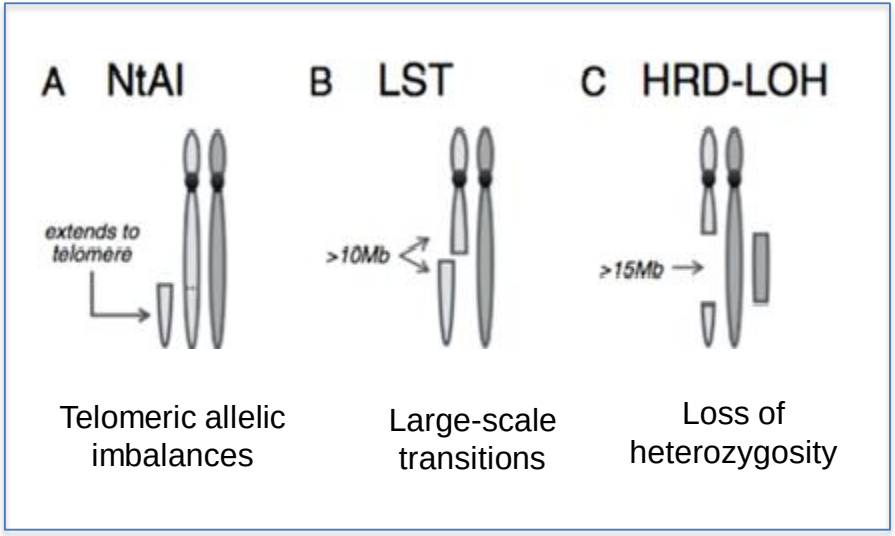
Homologous Recombination Deficiency (HRD) score

LGS HR intact



HGS HR deficient BRCA2mut

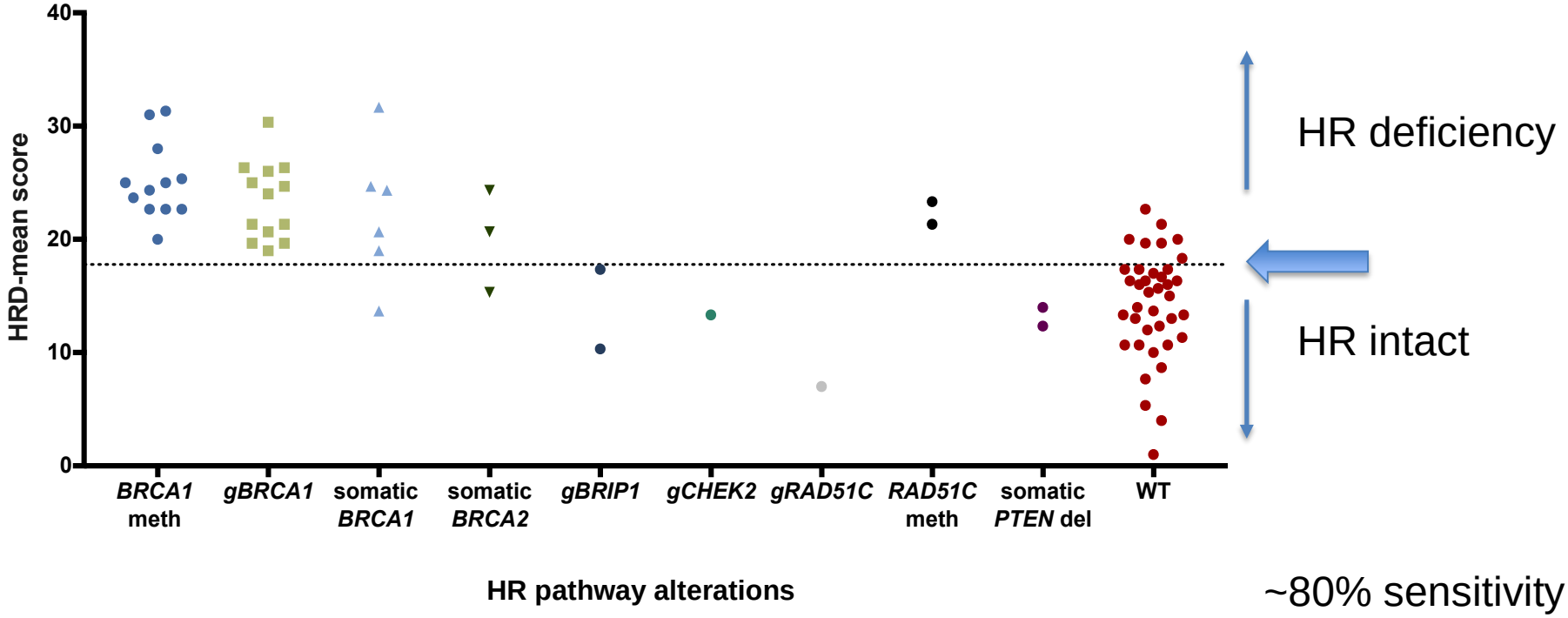




- Loss of HR lead to chromosomal structural rearrangement = genomic scar
- 3 SNP array based genomic lesion scores associated with *BRCA1/2*^{mut}
- HRD score - derived by computing the arithmetic mean of the three genomic lesion scores

Timms *et al* 2014 Biomarker Research
Marquard *et al* 2015 Breast Cancer Research

HRD predictive model based on ovarian cancer cases in the ICGC whole genome sequencing study

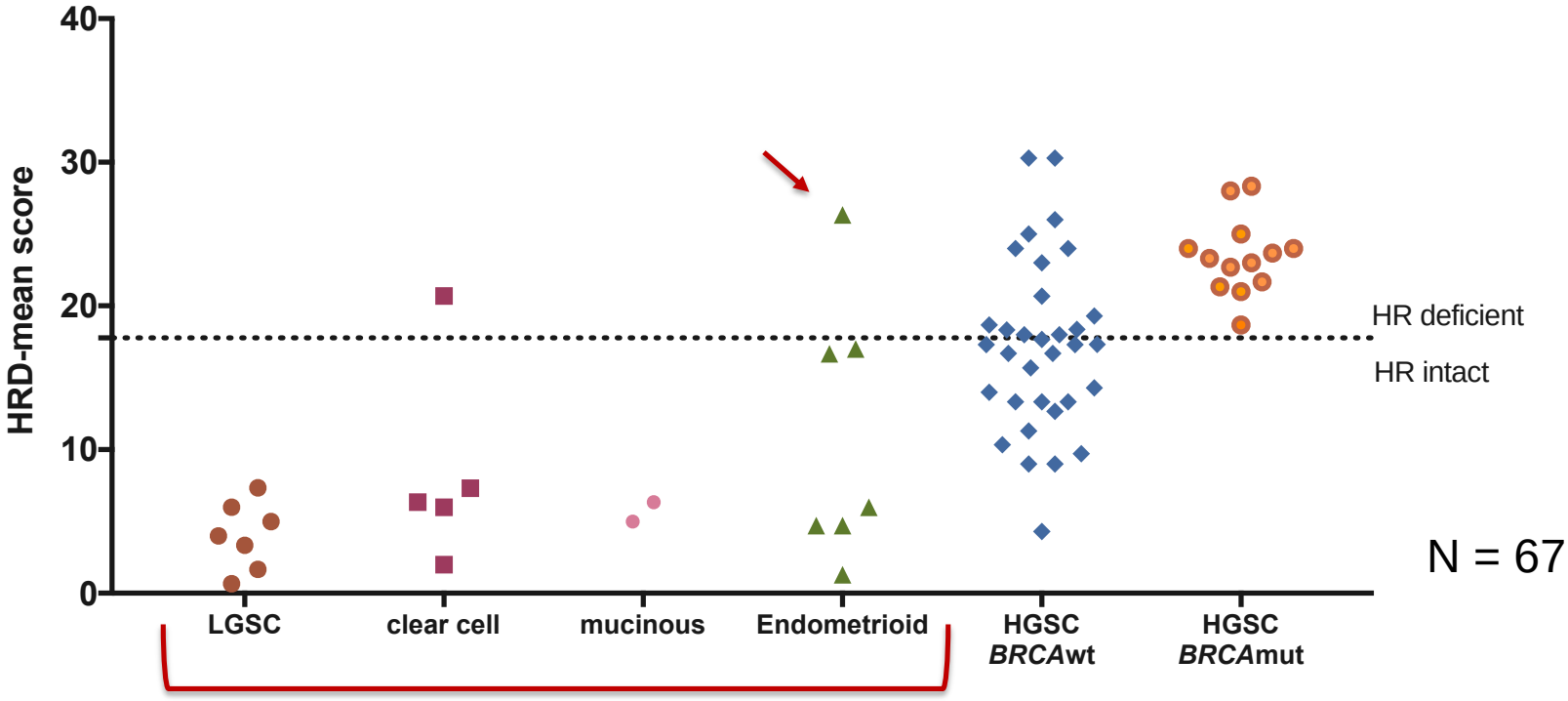


~80% sensitivity

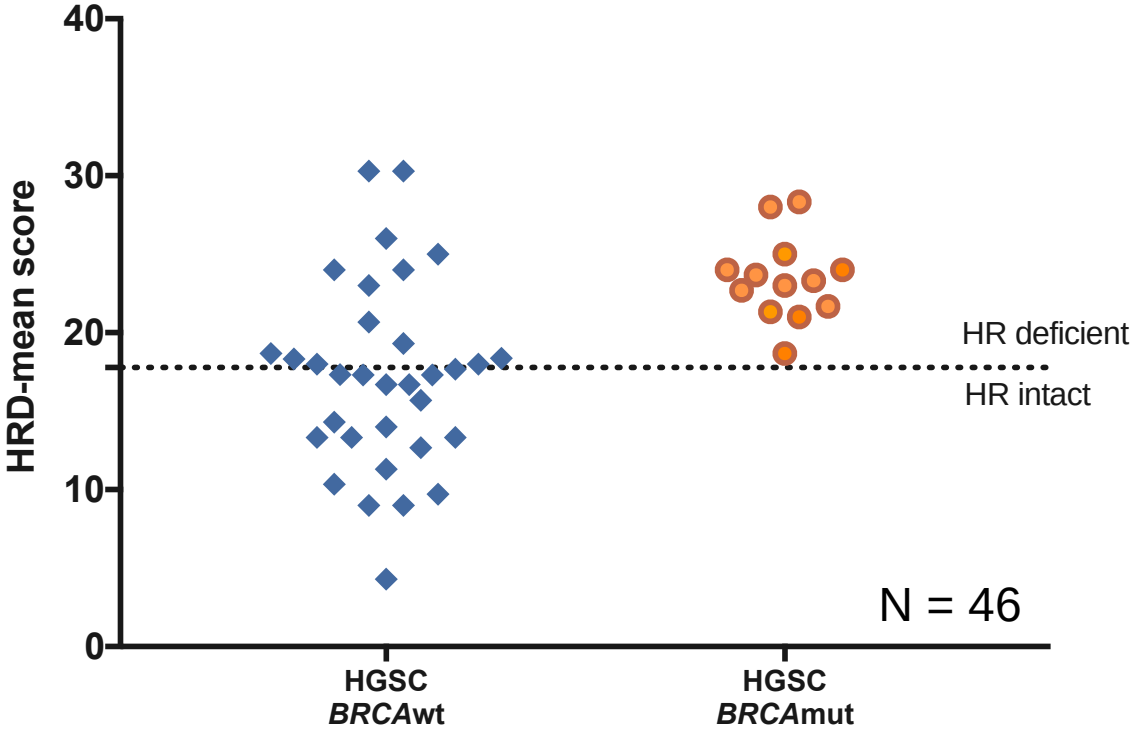
Swetansu Pattnaik

Patch *et al*, Nature 2015; 521 (7553):489-94

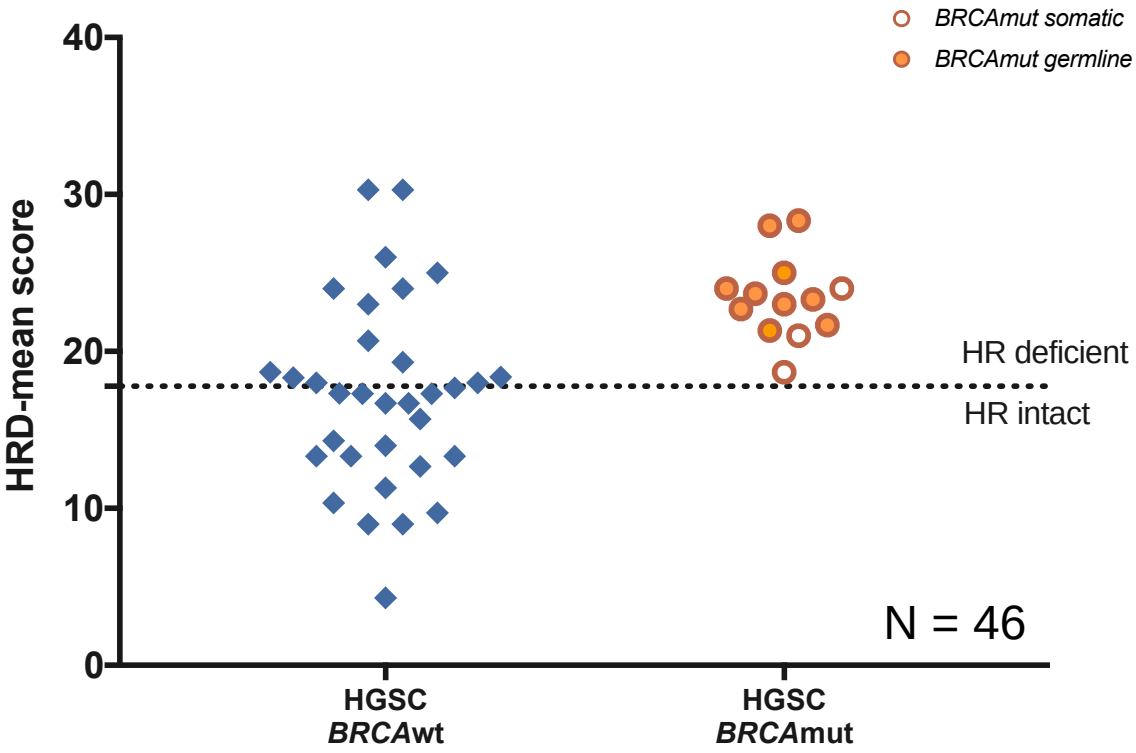
Distribution of HRD score among ovarian cancer histological subtypes in INOVATe



Distribution of HRD score in HGSC

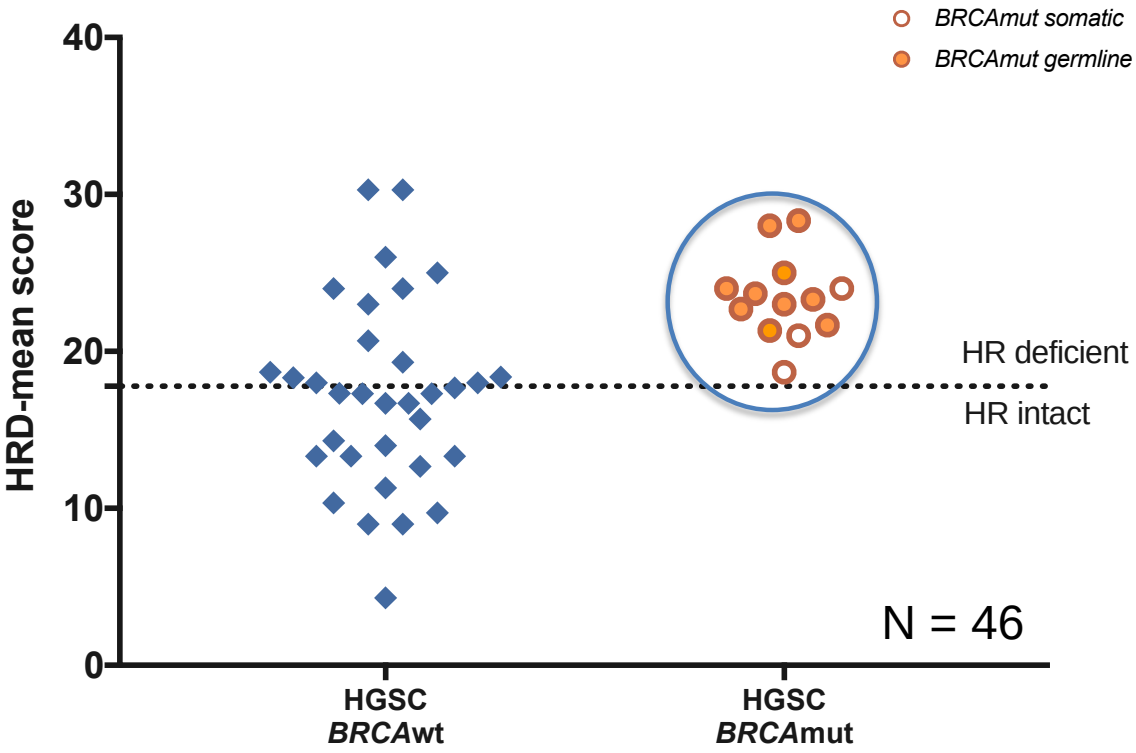


Distribution of HRD score in HGSC



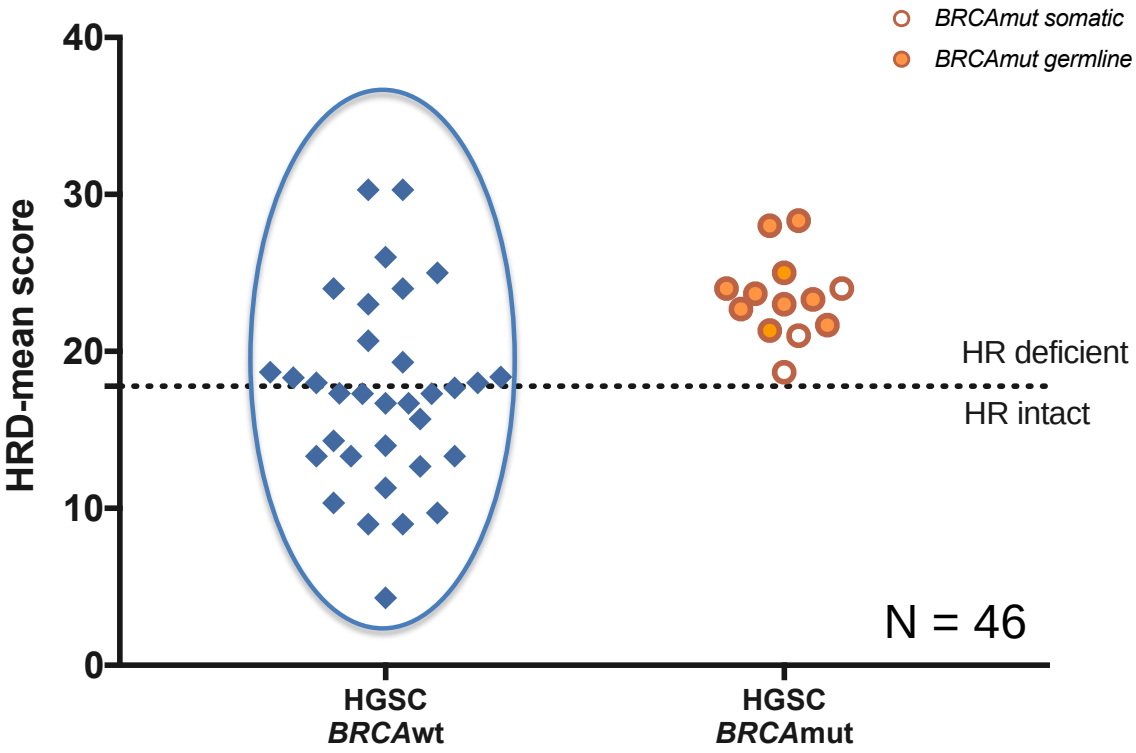
29.5% (13/46) *BRCA1/2*^{mut}

Distribution of HRD score in HGSC



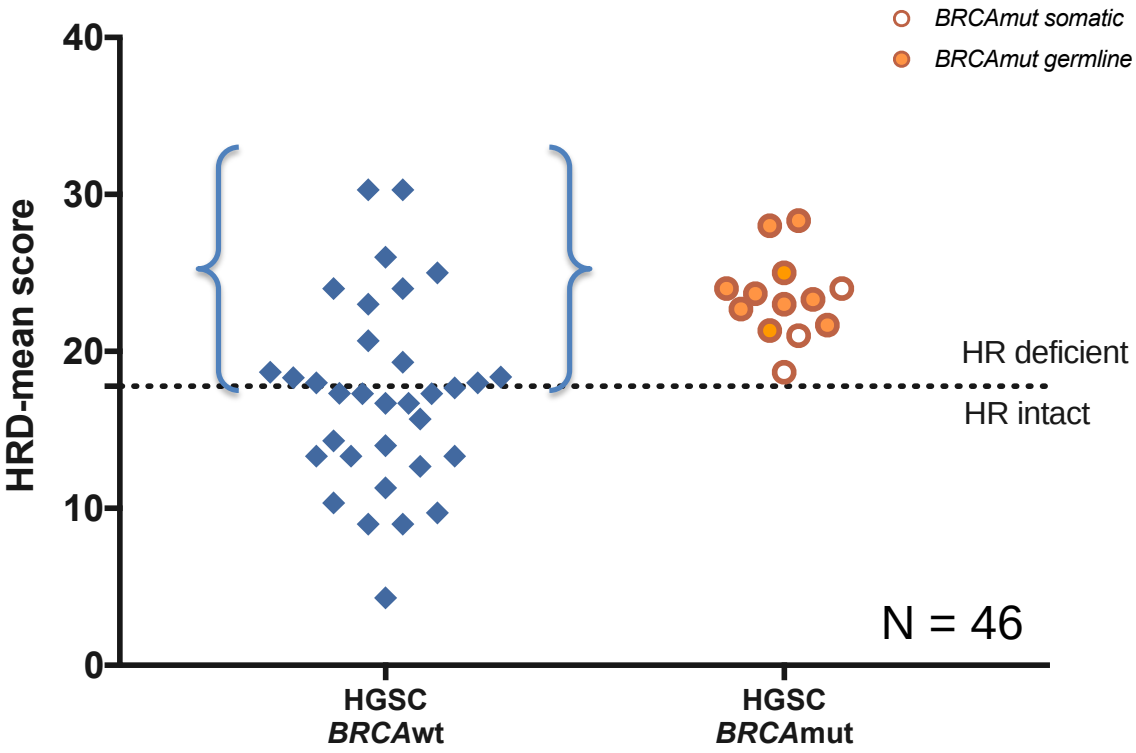
All *BRCA1/2*^{mut} cases showed evidence of HR deficiency

Distribution of HRD score in HGSC



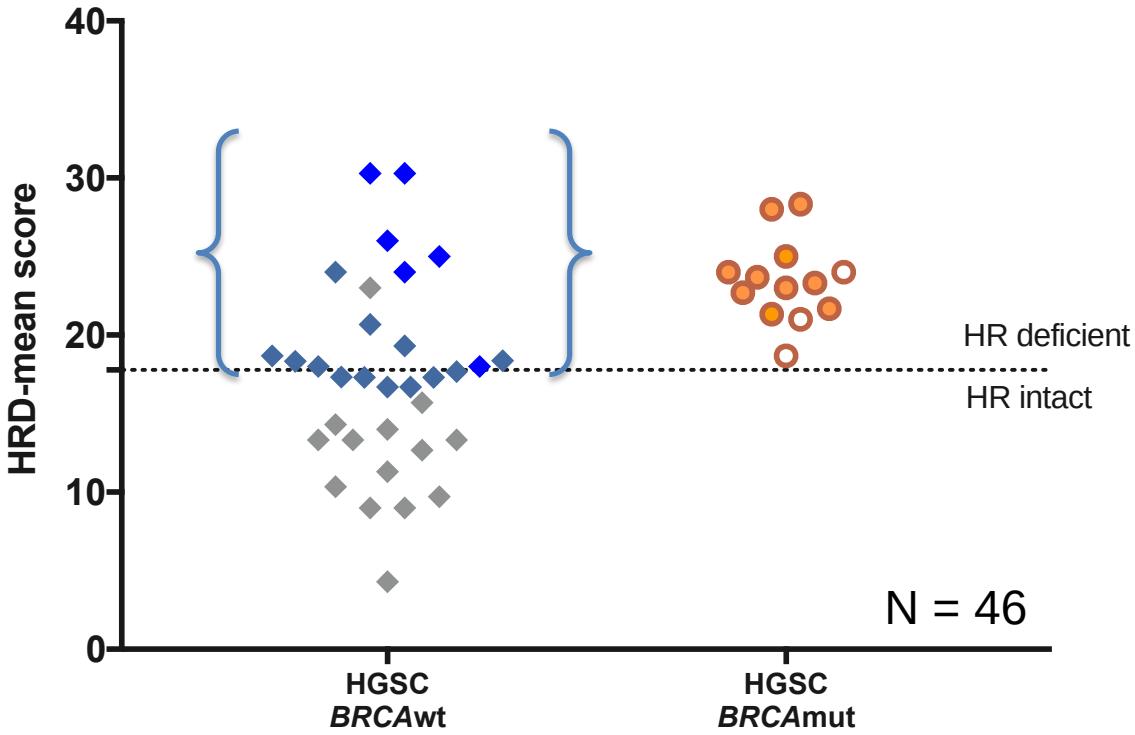
72% (33/46) of
HGSC BRCA1/2^{wt}

Distribution of HRD score in HGSC



42% shows evidence of HR deficiency (14/33)

Distribution of HRD score in HGSC



- *BRCA1 methylation not tested*
- *BRCA1 meth*
- *BRCA1 unmethylated*
- *BRCA^{mut} somatic*
- *BRCA^{mut} germline*

6/19 BRCA1 methylation

?alterations in other HR genes

Custom panel genes: *ATM, CHEK2, PALB2, RAD51C, RAD51D, BRIP1*

Response to PARPi?

Alex Dobrovic

PARP inhibition in non-*BRCA* HRD

PARP Inhibitor	Trial	Population group	PFS HR (95% CI)
Niraparib	ENGOT-OV16/NOVA	*BRCA1/2* ^{mut}	0.27 (0.17-0.41)*
		HRD-positive, non-germline *BRCA* mutated	0.38 (0.24-0.59)*
		BRCA1/2 ^{wt} and HR intact	0.45 (0.34-0.61)*
Rucaparib	ARIEL 3	*BRCA1/2* ^{mut}	0.23 (0.16-0.34)**
		HRD assay positive (*BRCA* ^{wt} and high-LOH)	0.32 (0.24-0.42)**
Olaparib	EMBRACE	Non-germline *BRCA*-mutated: *PALB2, ATM, ATR, RAD51*	
		BRCA1 methylated	

*P value <0.001; **P value <0.0001

HRD score assay

- HRD score was able to identify *BRCA*-altered and non-*BRCA* altered HR deficient cases

Limitations:

- Threshold for identifying HRD needs to be validated (current threshold 80% sensitivity)

- Does not identify *BRCA* reversion or loss of methylation
  - Functional assays in relapsed cases eg. *RAD51c* foci

- SNP array based: current assay only on Fresh/Frozen, will need to translate to FFPE tissue
  - NGS based

Conclusion

- Tumour testing of *BRCA* mutation status and germline clinical testing were highly concordant. Tumour testing identified additional somatic *BRCA1/2*^{mut} cases

- HRD score was able to identify all *BRCA1/2*^{mut} cases and other *BRCA1/2*^{wt} HR-deficient cases. These patients may benefit from PARPi treatment.

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