Abstract# 3132: Reversion Mutations in *BRCA1 or BRCA2* genes: Resistant Mechanism(s) in Patients Treated with Platinum-Based Agents or Poly (ADP-ribose) Polymerase (PARP) Inhibitors

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Background:

- Defects in genes that control homologous recombination DNA repair are common in some tumors (including mutations in *BRCA1/2* genes)
- There are a number of treatment recommendations based on these defects including platinum therapy and/or PARP inhibition
- Reversion mutations (RM) in homologous recombination pathway genes have been reported in tumors that become resistant to platinum therapy or PARP inhibition
- The purpose of this study was to evaluate the prevalence of RM in *BRCA1/2* genes in a large cohort of patients with solid tumor malignancies

Methods:

- We retrospectively analyzed molecular data in tumor samples that DNA (underwent NextSeq, 592 genes; NovaSeq, whole-exome) and RNA (NovaSeq, whole transcriptome) were available
- RM were detected by a board-certified geneticist
- The variants were called only if the patient had been treated with a platinum-based chemotherapy or PARP inhibition

Table 1- Number of detected RM in different cancer types

Cancer Types	BRCA1	BRCA2	Total
Ovarian Cancer	17	6	23
Breast Cancer	7	10	17
Endometrial Cancer		4	4
Pancreatic Cancer	2		2
Cholangiocarcinoma	1	1	2
Prostate Cancer		3	3
Cervical Cancer	1		1
Cancer of Unknown Primary		1	1
Neuroendocrine tumor		1	1
Total	28	26	54

Results:

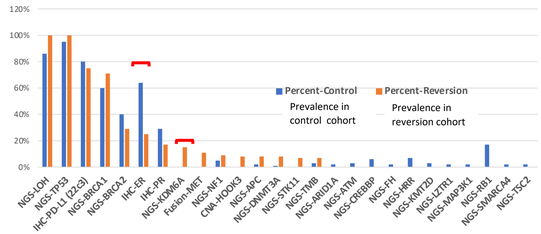
- Profiled 118,000 solid tumors and found RM in 54 patients' tumors in *BRCA1/2*
  - RM reported in ovarian cancer (1.5%), breast cancer (2.4%), endometrial and pancreatic cancer (1%), cholangiocarcinoma (2.5%), prostate cancer (1.3%), and cervical cancer (1.4%)
  - 17 in *BRCA1* and 6 in *BRCA2* in ovarian cancer
  - 7 in *BRCA1* and 10 in *BRCA2* in breast cancer
- Molecular differences were seen in ovarian high-grade serous tumors with or without *BRCA1/2* RM
- Detailed clinical data were available in 29/54 patients (17 RM in *BRCA1* and 12 in *BRCA2*)
  - 7 had received prior platinum-based chemotherapy (carboplatin or cisplatin), 7 patients were treated with PARP inhibitors (olaparib or rucaparib), 7 patients received both
  - Notably, 5 patients had been treated with carboplatin (n = 2, ovarian), olaparib (n = 1, breast), or both agents (n = 2, ovarian and prostate) after the detection of RM

Conclusions:

- Although RM are rare events, repeating molecular tumor profiling at the time of treatment resistance may help guide therapy selection in the refractory disease setting

Figure 2: Ovarian high-grade serous *BRCA1/2* mutant tumors with or without reversions

- A consecutive cohort of 87 high-grade ovarian cancers with pathogenic *BRCA1/BRCA2* mutations without RM were chosen as control for molecular comparison; comparison with 14 reversion high grade serous ovarian cases.
- *BRCA1/2* RM trends to have lower ER expression and higher *KDM6A* mutation rate. No *RB1* mutations seen in reversion cases.



Gain-of-function *TP53* mutations trends to have higher chance of BRCA reversions

	TP53 mutations, p=0.048	
Category	GOF	Non-GOF
Control	19	65
Reversion	7	7

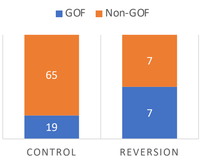
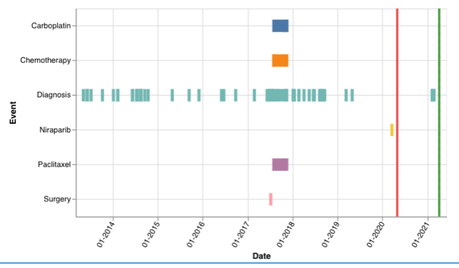


Figure 3: Example patient treatments and outcome from real-world-evidence (first vertical line: time of tumor profiling; second vertical line: last day of contact)

Left: example ovarian cancer patient detected with *BRCA1* RM after platinum and PARPi treatments
Right: example prostate cancer patient receiving rucaparib and platinum agents after detection of *BRCA2* RM



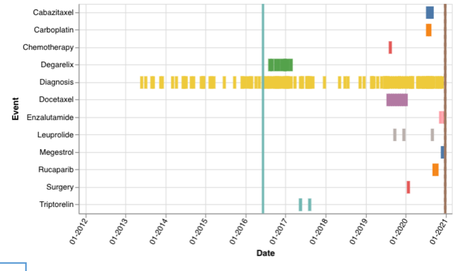
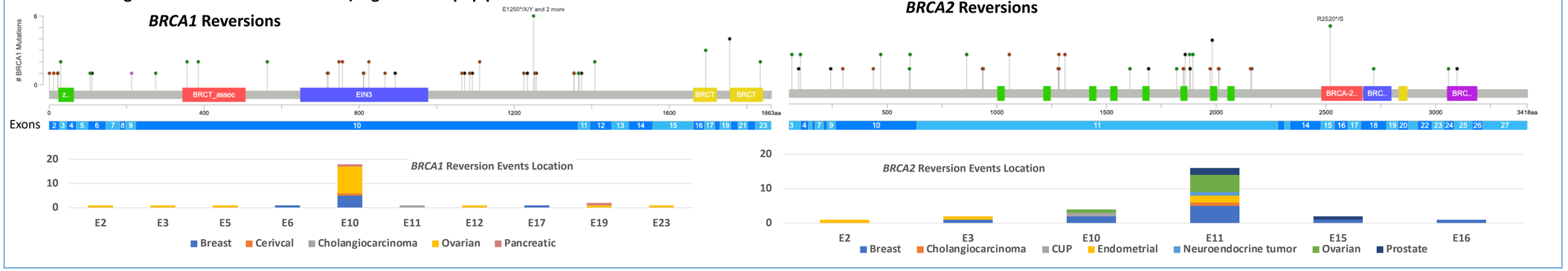


Figure 1- Identified RM in *BRCA1/2* genes: Lollipop plots and exon location of RM



Selected References:

- Jacob SL, et al. Case Reports. Heliyon. 2020; 6(5):e03841
- Pettitt SJ, et al. Can Discov. 2020; DOI: 10.1158/2159-8290
- Brenda K, et al. JCO Prec Oncol. 2018; DOI: 10.1200/PO.17.00044
- Lin KK, et al. Cancer Discov. 2019; doi: 10.1158/2159-8290.CD-18-0715
- Ganesan S, et al. JCO Precis Oncol. DOI: 10.1200/PO.18.00001
- Waks AD, et al. Ann Oncol. 2020; 31(5):590-598
- Cheng HH, et al. JCO Precis Oncol. 2018; 2:PO.17.00169
- cBioPortal. MutationMapper

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