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Cancer Center

Germline and Somatic DNA Repair Defects in Prostate Cancer

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Objectives

- The concept of synthetic lethality of in the context of BRCA-deficient tumors
  - PARP inhibition
- Basics: ovarian cancer
  - Role of germline BRCA-status in treatment
- Resistance to PARP inhibition
  - Reversion mutations
- Journal article: detection of reversion mutations in cfDNA
- Why this matters

Germline BRCA Mutation

- Prostate Cancer is a BRCA associated malignancy
  - along with Breast, Ovarian, and Pancreatic Cancers
- At risk populations include Ashkenazi Jews, Nordic populations, Italians, French, Hispanics, and African Americans

	% of localized Prostate Cancers[1,2]	Relative Risk of Prostate Cancer in Carriers[1-3]
BRCA 1	0.44%	3.4
BRCA 2	1.2%	8.6

[1] Kote-Jarai Z, Et al. Br J Can 2011;105:1230-1234. [2] Leongamornlert D, et al. Br J Can 2012;106:1697-1701.
[3] Breast Cancer Linkage Consortium. JNCI 1999;91:1310-1316.

BRCA 2

- Associated with Higher Gleason Score, higher stage, and younger age of diagnosis[4]
- BRCA 2 carriers are considered High Risk by NCCN guidelines
  - PSA screening should be discussed starting at Age 40

[4]Castro E, et al. JCO (2013) 31(14):1748-1757.

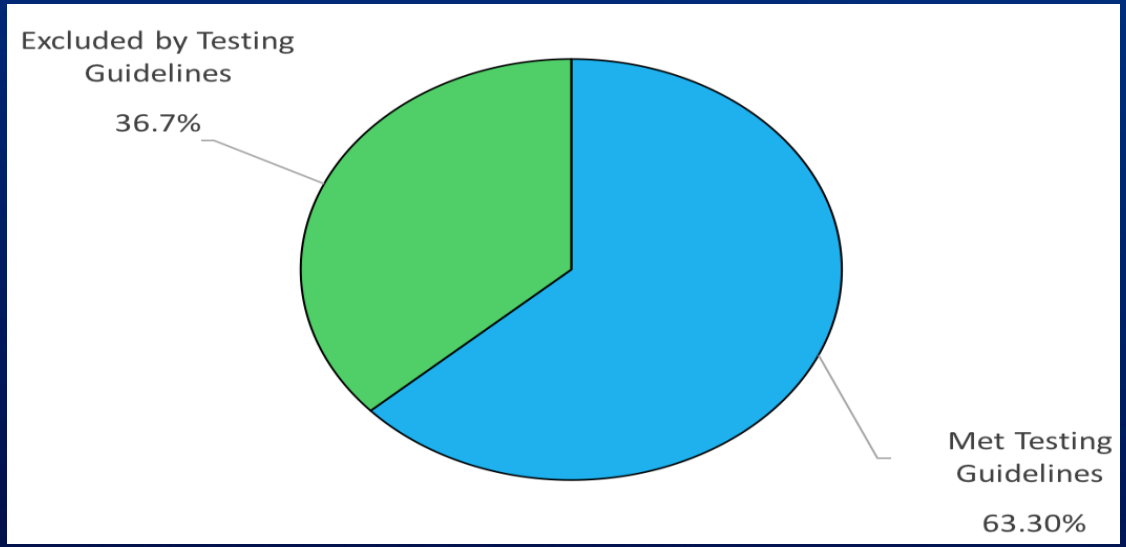
Screening Guidelines Fall Short

Examined 1158 localized PC patients with germline DNA testing

199 patients had a high risk germline mutation (BRCA 1 or 2, ATM, TP53, others)

Patients were compared to NCCN criteria for germline testing

CONCLUSION: Genetic testing guidelines and Gleason scores do not reliably identify PCa patients for the presence/absence of high risk germline variants



Nicolosi P, et al. JCO May 2017 35(15s);5009.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

C.C. Pritchard, J. Mateo, M.F. Walsh, N. De Sarkar, W. Abida, H. Beltran, A. Garofalo, R. Gulati, S. Carreira, R. Eeles, O. Elemento, M.A. Rubin, D. Robinson, R. Lonigro, M. Hussain, A. Chinnaiyan, J. Vinson, J. Filipenko, L. Garraway, M.-E. Taplin, S. AlDubayan, G.C. Han, M. Beightol, C. Morrissey, B. Nghiem, H.H. Cheng, B. Montgomery, T. Walsh, S. Casadei, M. Berger, L. Zhang, A. Zehir, J. Vijai, H.I. Scher, C. Sawyers, N. Schultz, P.W. Kantoff, D. Solit, M. Robson, E.M. Van Allen, K. Offit, J. de Bono, and P.S. Nelson

Table 3. Germline DNA-Repair Gene Mutations in Seven Metastatic Prostate Cancer Case Series.

Case Series	Description	Patients	Patients with Mutations
		no.	*no. (%)*
1	Stand Up To Cancer–Prostate Cancer Foundation discovery series	150	15 (10.0)
2	Stand Up To Cancer–Prostate Cancer Foundation validation series	84	9 (10.7)
3	Royal Marsden Hospital	131	16 (12.2)
4	University of Washington	91	8 (8.8)
5	Weill Cornell Medical College	69	7 (10.1)
6	University of Michigan	43	4 (9.3)
7	Memorial Sloan Kettering Cancer Center	124	23 (18.5)
Total		692	82 (11.8)

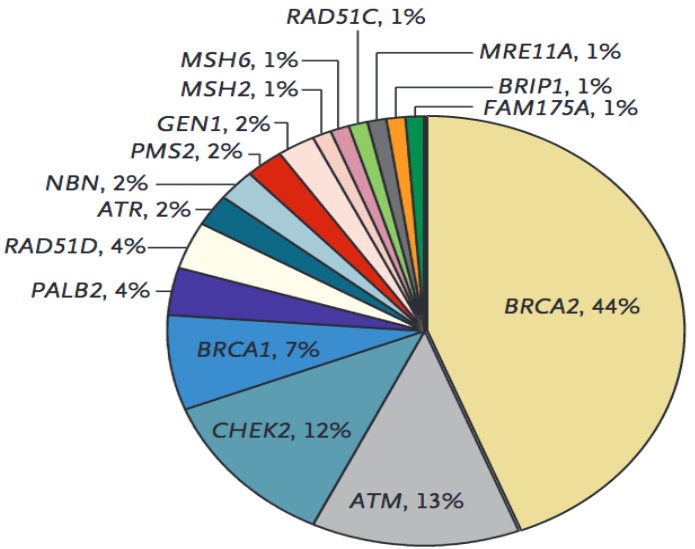
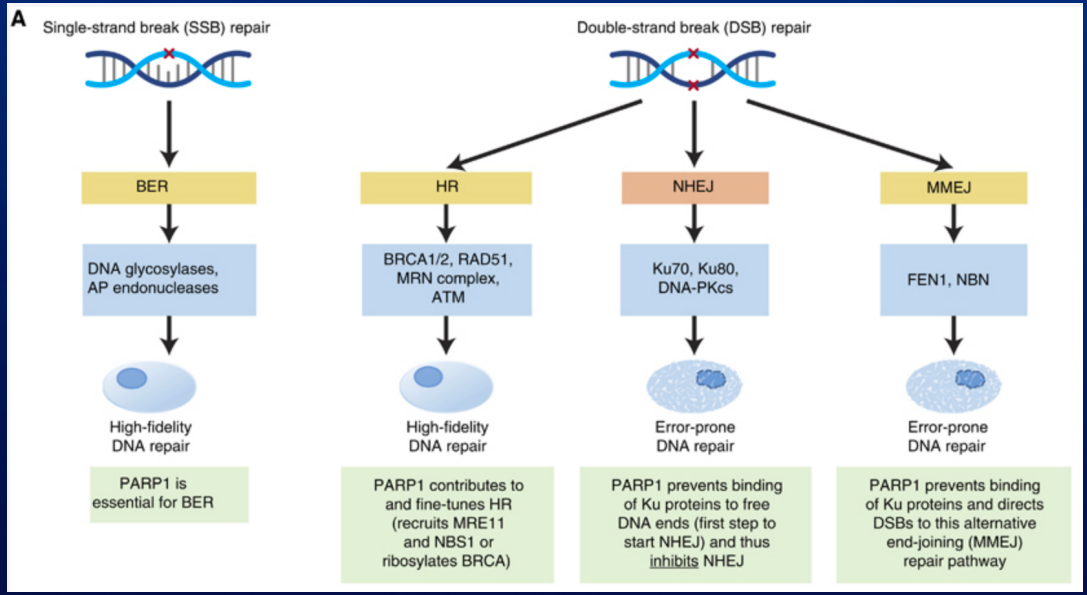


Figure 2. Distribution of Presumed Pathogenic Germline Mutations.
Shown are mutations involving 16 DNA-repair genes. Four genes did not have any pathogenic mutations identified and are not included in the distribution.

The DNA damage response is critical to genomic integrity and cellular survival

- DNA double strand breaks (DSBs) trigger homologous recombination repair (HRR)
  - High fidelity; BRCA-dependent
    - Rad51
  - BRCA-deficient cells demonstrate chromosomal instability as they rely on error prone repair mechanisms (non-homologous end joining, NHEJ)

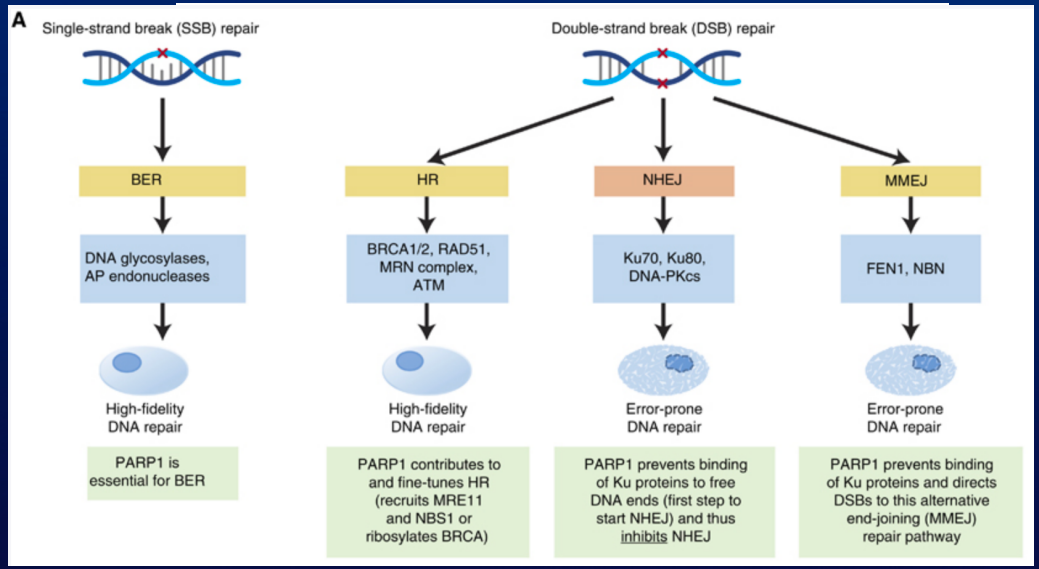
- Poly(ADP-ribose) polymerases (PARP)
  - PARP 1 most abundant; studied mostly in the context of DNA base excision repair (BEP)
  - DNA single strand breaks (SSBs)
  - Plays role in HRR; inhibits NHEJ



Konecny and Kristeleit,

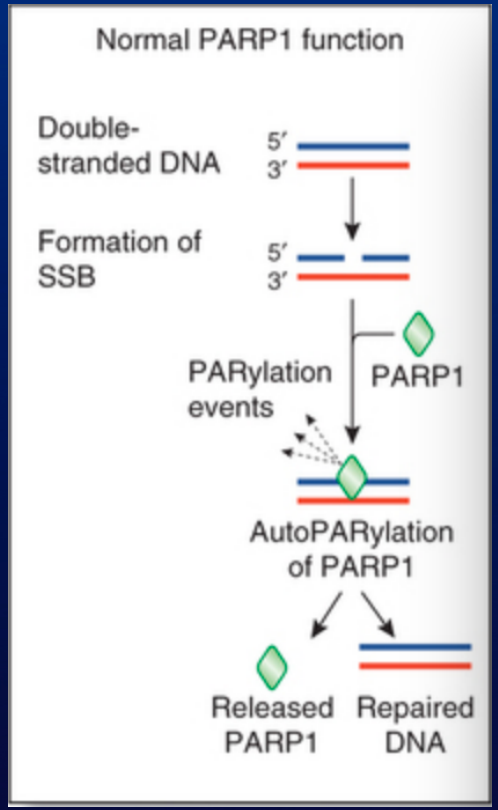
BRCA1- and BRCA2-deficient tumors and "synthetic lethality"

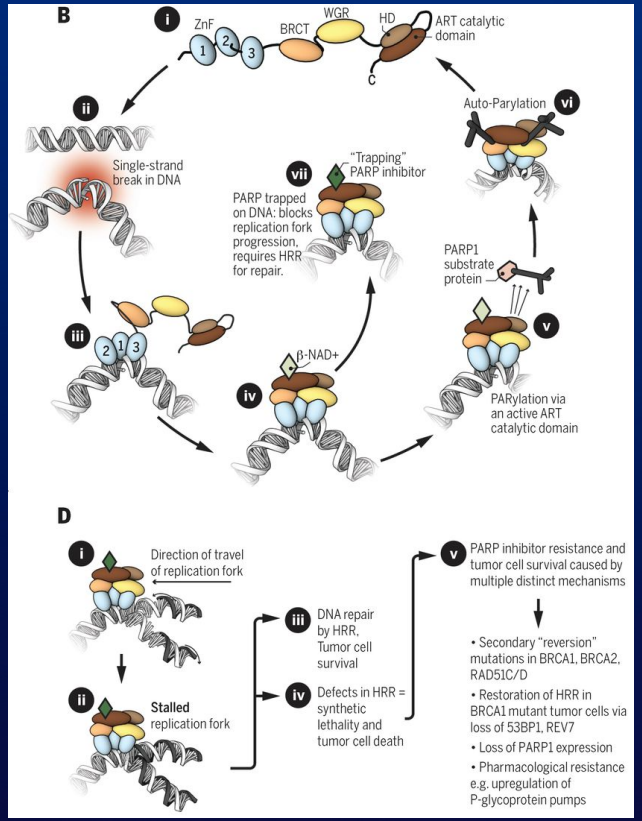
- Deleterious germline mutations in BRCA1 and BRCA2 are associated with high risk of certain tumors
  - Breast cancer
  - Ovarian cancer
  - Prostate cancer
- Synthetic lethality



Konecny and Kristeleit, BJC 2016
Lord and Ashworth, Nature Medicine 2013

Poly(ADP-Ribose) Polymerase (PARP) enzymes are critical to the DNA damage response (DDR)





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Lord and Ashworth, Nature Medicine 2013, Science 2017

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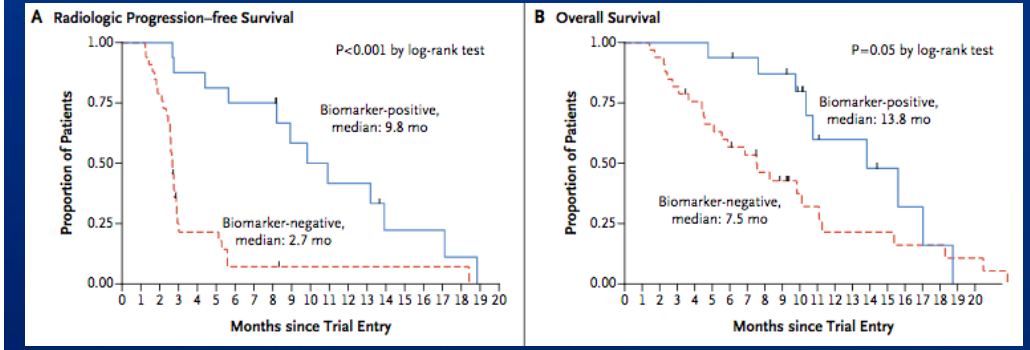
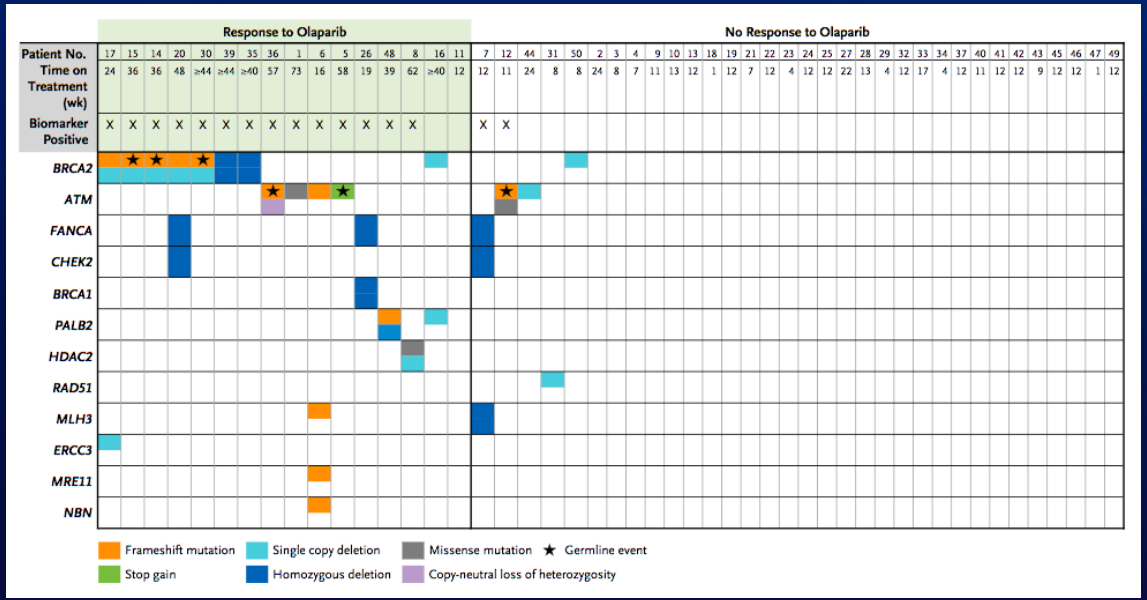
J. Mateo, S. Carreira, S. Sandhu, S. Miranda, H. Mossop, R. Perez-Lopez, D. Nava Rodrigues, D. Robinson, A. Omlin, N. Tunariu, G. Boysen, N. Porta, P. Flohr, A. Gillman, I. Figueiredo, C. Paulding, G. Seed, S. Jain, C. Ralph, A. Protheroe, S. Hussain, R. Jones, T. Elliott, U. McGovern, D. Bianchini, J. Goodall, Z. Zafeiriou, C.T. Williamson, R. Ferraldeschi, R. Riisnaes, B. Ebbs, G. Fowler, D. Roda, W. Yuan, Y.-M. Wu, X. Cao, R. Brough, H. Pemberton, R. A'Hern, A. Swain, L.P. Kunju, R. Eeles, G. Attard, C.J. Lord, A. Ashworth, M.A. Rubin, K.E. Knudsen, F.Y. Feng, A.M. Chinnaiyan, E. Hall, and J.S. de Bono





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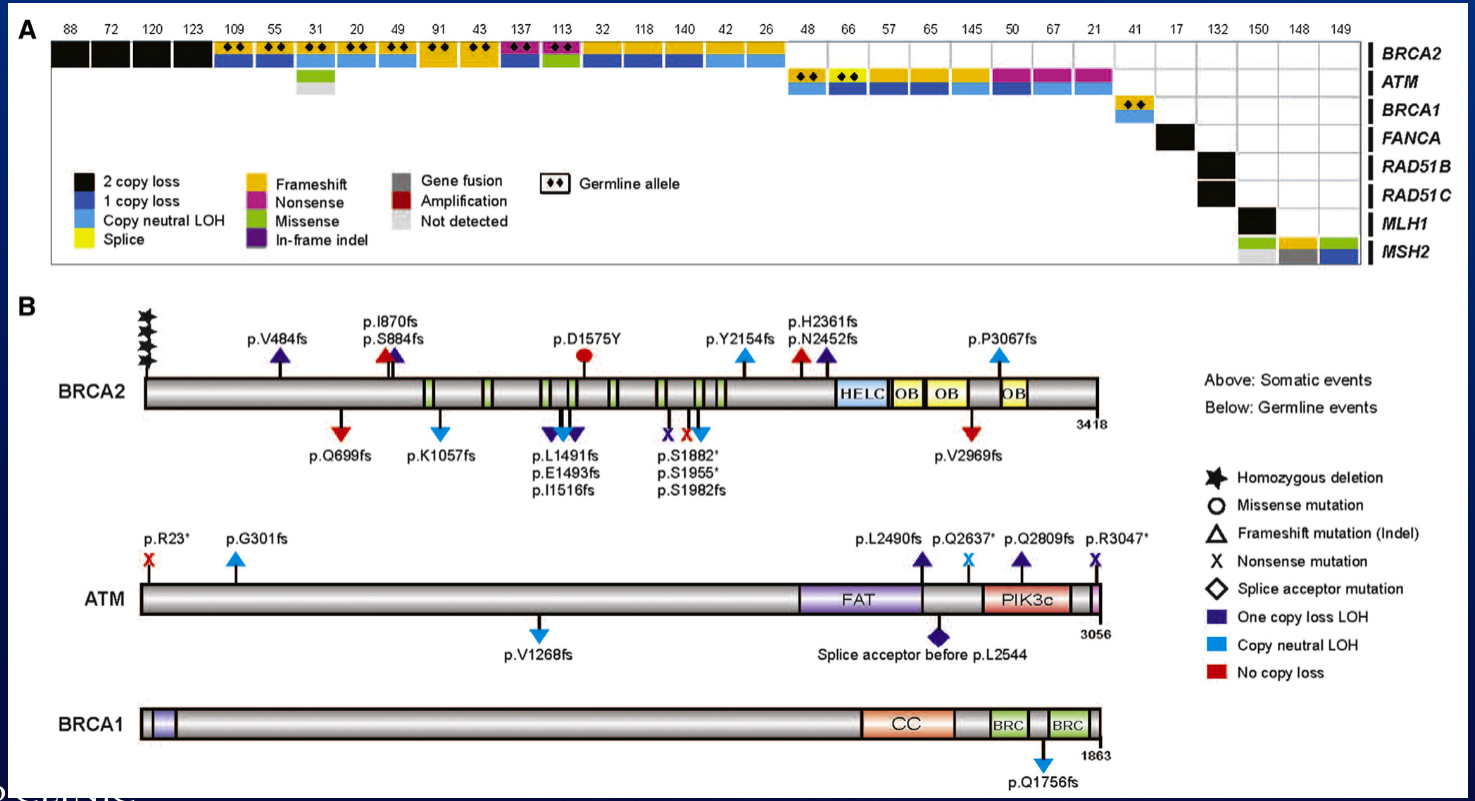
mCRPC: somatic and germline DDR defects



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Robinson, Van Allen et al

DDR defects are common in advanced prostate cancer

- 20-25% of metastatic prostate cancer may harbor defects in DDR genes
- Clinical trials targeting DRD are ongoing (and being developed)
  - Niraparib (Jannsen), Olaparib (Astra Zeneca), Rucaparib (Clovis), Talazoparib (Pfizer)

