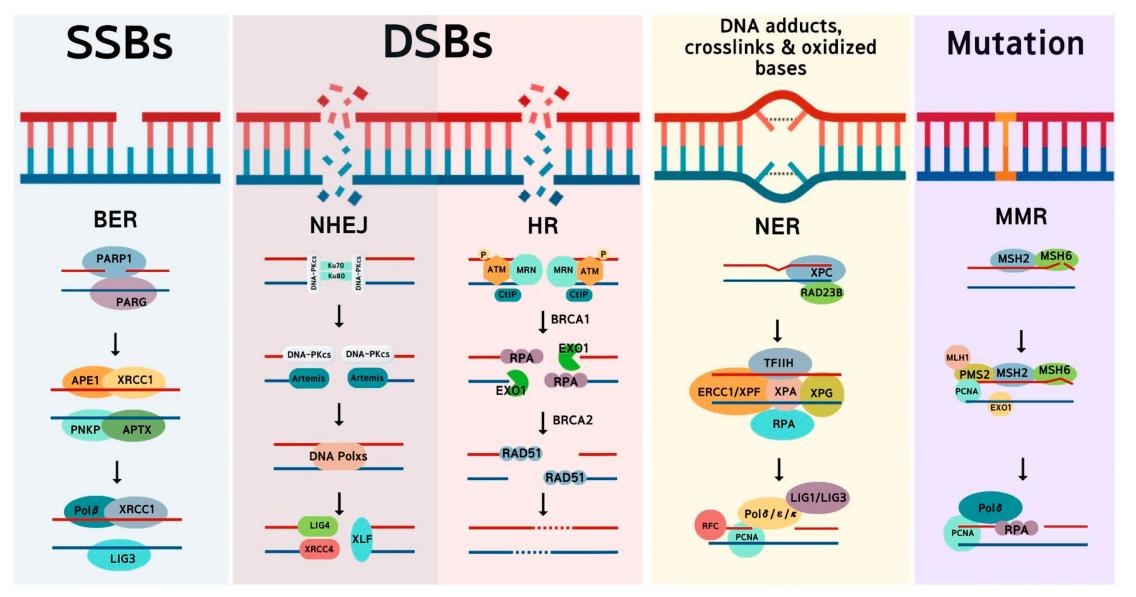
Evaluating and Targeting Defects in DNA Damage Repair

Mark Robson, MD, FASCO

March 29, 2025 MaTOS Summit, Charlotte, NC

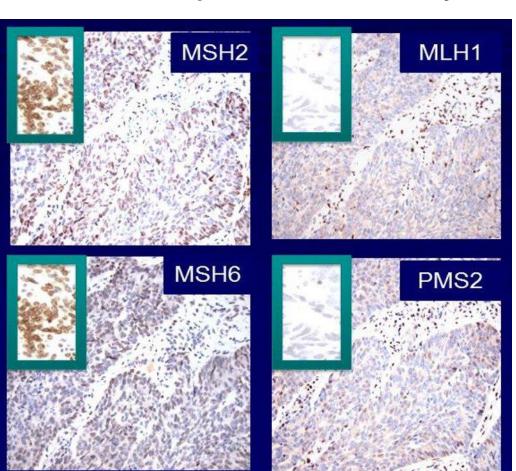


Point 1: Different Repair Pathways for Different Types of DNA Damage



2

Point 2: Different DNA Damage Repair Defects Have Different "Phenotypes"



Mismatch Repair Protein Deficiency

Microsatellite Instability

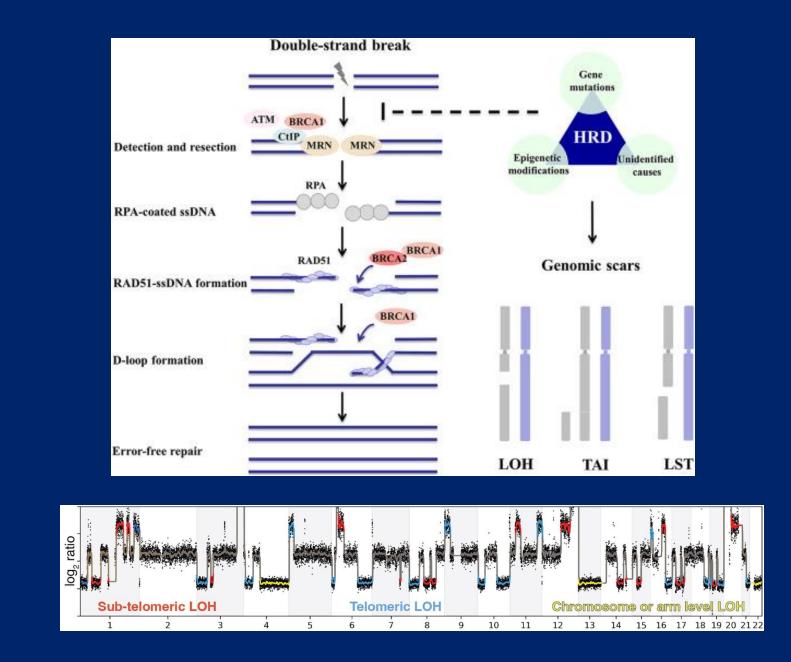
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Point 2: Different DNA Damage Repair Defects Have Different "Phenotypes"

HRD leads to "genomic scars"

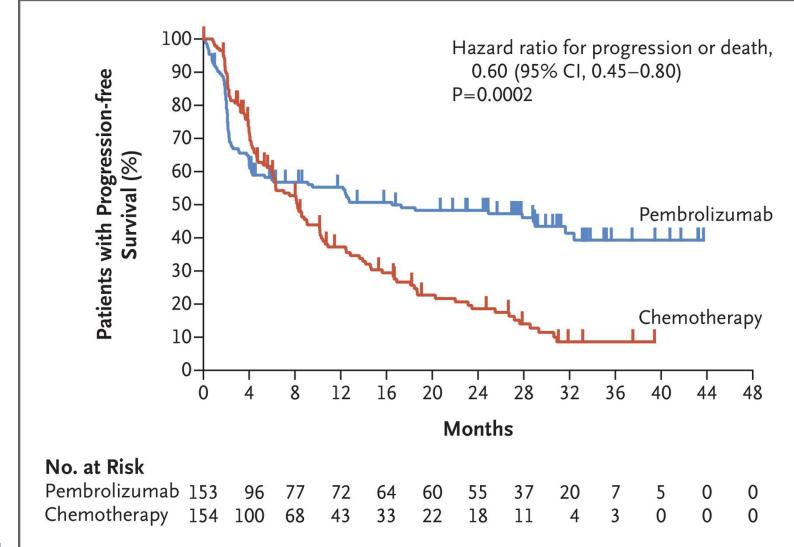


Mutational Signatures Reflect Mechanism of Carcinogenesis

Some mutational signatures reflect specific DNA damage repair defects (e.g. HRD)



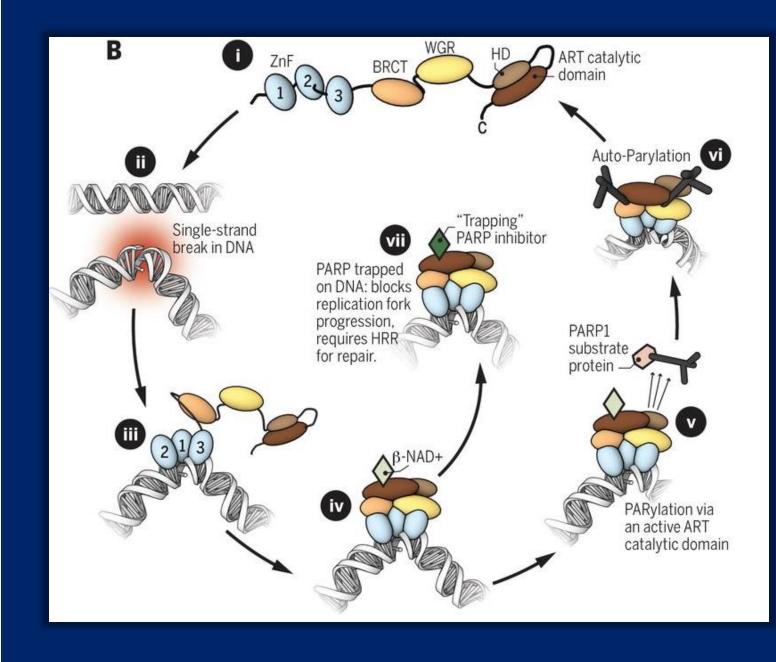
Treatment May Target the Result ("Phenotype") of Repair Defect



Andre et al, DOI: 10.1056/NEJMoa2017699M

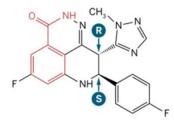
Treatment may target the PROCESS of repair deficiency

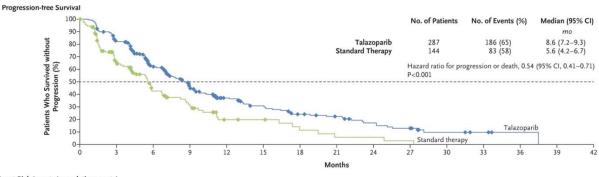
Example: Synthetic lethality of PARPi in HR-deficient cells



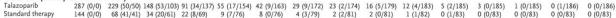
Treatment May Target the PROCESS of Repair Deficiency

Talazoparib



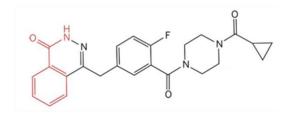


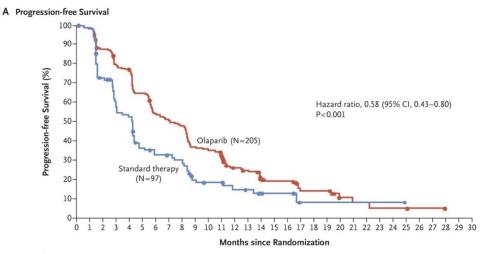




Litton et al, NEJM 2018

Olaparib





No. at Risk

 Olaparib
 205 201177159154129107100
 94
 73
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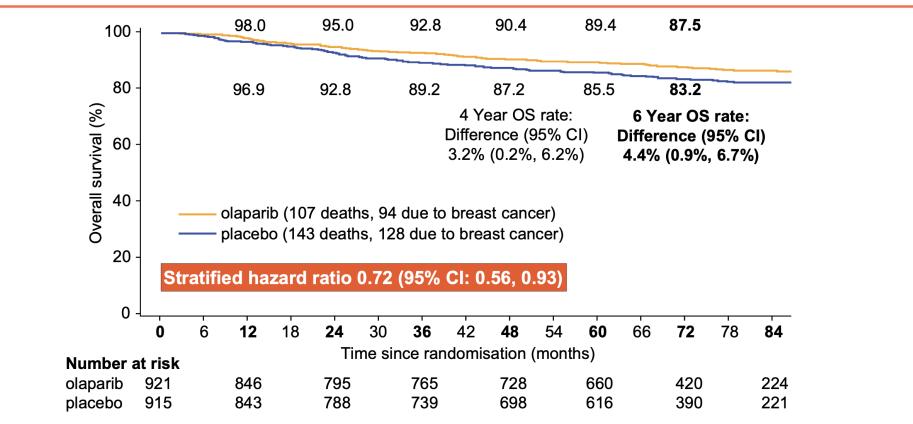
Robson et al, NEJM 2017

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Outcomes of OlympiA 10 years after FPI

Analysis of OS (ITT)





Garber et al, SABCS 2024

Outcomes of OlympiA 10 years after FPI

American Associati for Cancer Research **Triple negative** ER and/or PgR positive 87.2 82.9 80.7 77.5 92.8 91.4 100 100 93.5 89.3 86.0 83.1 81.6 80.0 Invasive disease-free survival (%) 80 80 81.3 75.3 73.5 70.8 88.2 77.5 72.0 69.7 67.7 89.4 81.9 76.9 60 60 40 40 olaparib (142 events) olaparib (35 events) placebo (211 events) placebo (47 events) Median follow-up: 5.7 years 20 Median follow-up: 6.3 years 20 Stratified hazard ratio 0.652 (95% CI: 0.526, 0.805) Stratified hazard ratio 0.681 (95% CI: 0.437, 1.051) 0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 6 12 18 24 30 36 42 48 54 60 66 72 78 84 0 0 Time since randomisation (months) Time since randomisation (months) Number at risk 105 53 Olaparib 751 579 514 306 168 140 131 124 116 15 636 544 463 178 Placebo 758 632 565 519 489 430 282 162 157 134 118 109 99 82 45 19

Analysis of IDFS by HR status

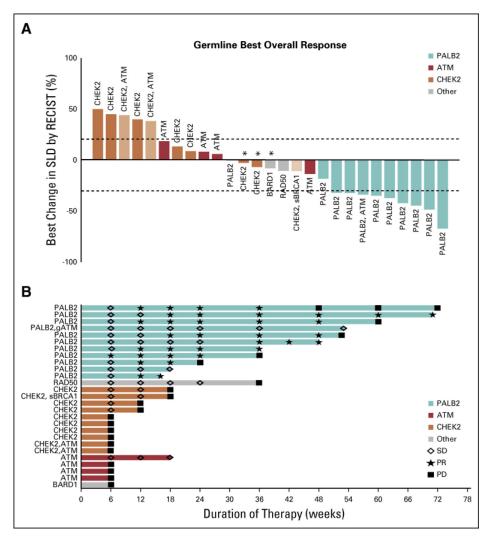
Garber wt al SABCS 2024

SAN ANTONIO BREAST CANCER

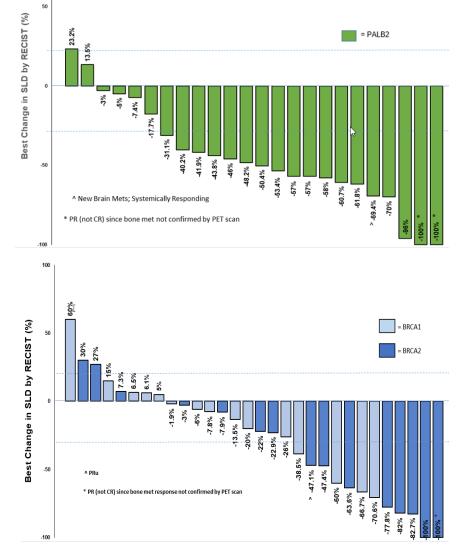
AACR

SYMPOSIUM

JT Health



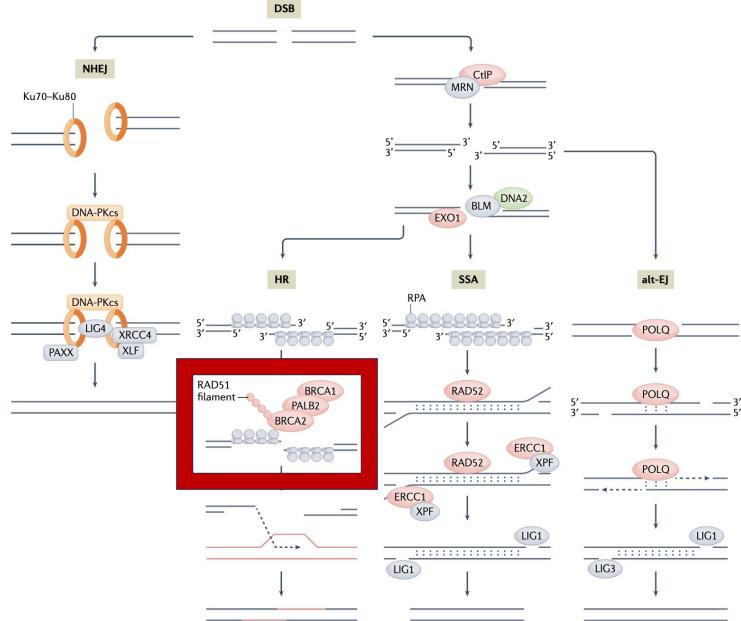
Tung N, Robson M et al, JCO 2021



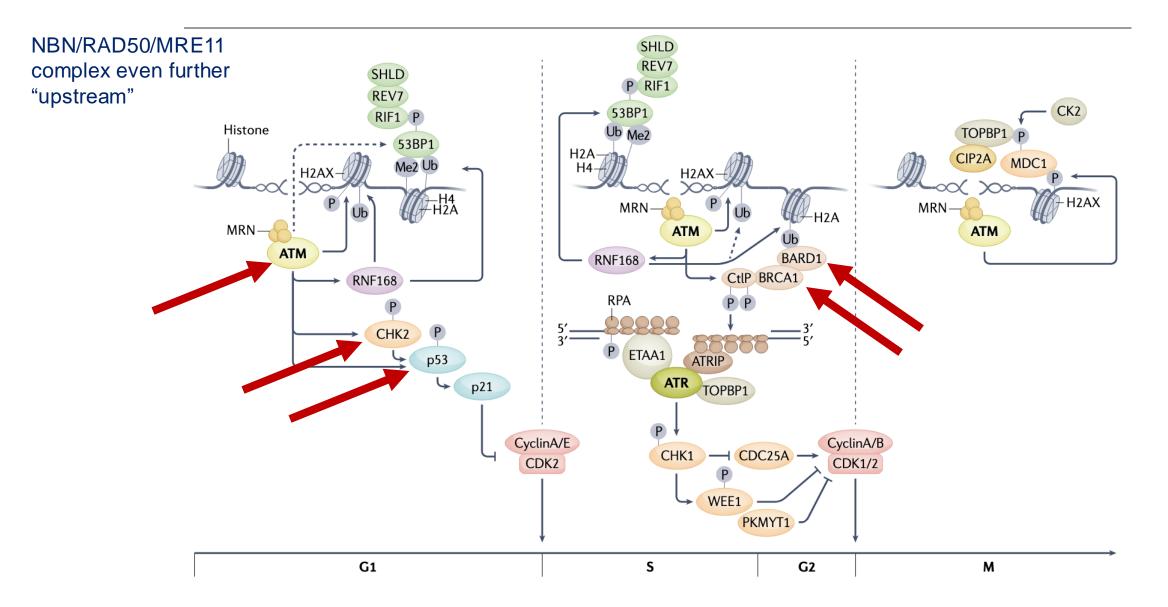
Tung N, Robson M et al, ASCO 2024

ORR 75%

ORR 37%



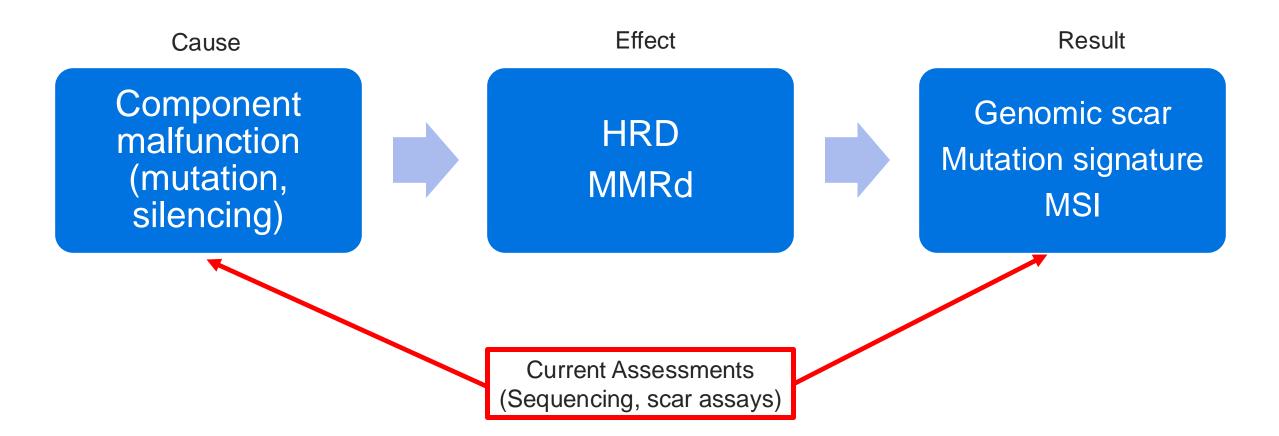
Groelly et al, Nature Cancer Reviews 2023



Groelly et al, Nature Cancer Reviews 2023

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Problem: How to measure the process

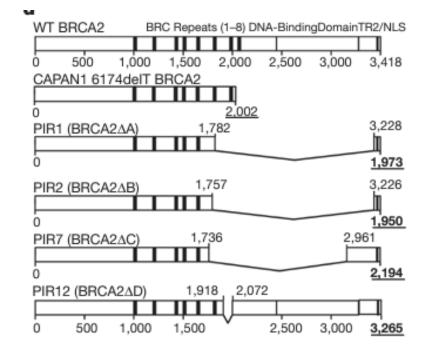


Multiple mechanisms of PARPi resistance

Resistance to therapy caused by intragenic deletion in *BRCA2*

Stacey L. Edwards¹, Rachel Brough¹, Christopher J. Lord¹, Rachael Natrajan¹, Radost Vatcheva¹, Douglas A. Levine², Jeff Boyd³, Jorge S. Reis-Filho¹ & Alan Ashworth¹

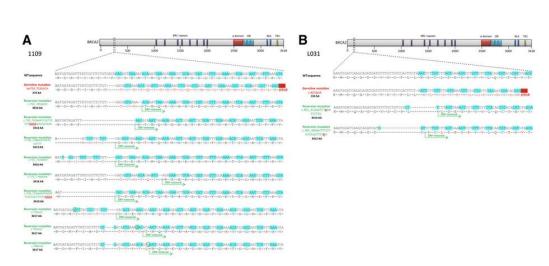
Nature 2008



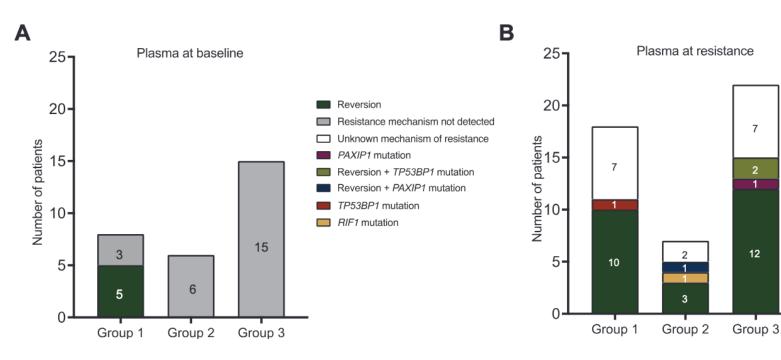
Diverse BRCA1 and BRCA2 Reversion Mutations in Circulating Cell-Free DNA of Therapy-Resistant Breast or Ovarian Cancer

Britta Weigelt¹, Iñaki Comino-Méndez², Ino de Bruijn¹, Lei Tian³, Jane L. Meisel^{4,5}, Isaac García-Murillas², Charlotte Fribbens^{2,6}, Ros Cutts², Luciano G. Martelotto¹, Charlotte K.Y. Ng^{1,7,8}, Raymond S. Lim¹, Pier Selenica¹, Salvatore Piscuoglio^{1,7}, Carol Aghajanian⁴, Larry Norton⁴, Rajmohan Murali¹, David M. Hyman⁴, Laetitia Borsu¹, Maria E. Arcila¹, Jason Konner⁴, Jorge S. Reis-Filho¹, Roger A. Greenberg³, Mark E. Robson⁴, and Nicholas C. Turner^{2,6}

Clin Cancer Res 2017



PARPi resistance mechanisms



12% 21% 6% Percent reversion mutations 7% 75% 16% 17% 22% 50% 10% 25% 45% 45% 0% BRCA1 BRCA2 Microhomology deletion Deletion Deletion (multiple exon) Insertion Substitution

100%

7

1

12

Group 1: de novo resistant Group 2: minimal response Group 3: response, then progression

Harvey-Jones et al, Ann Oncol 2024

Scars may remain ...



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Summary

- Not all defects in DNA damage repair are the same (DDR is a *very* broad term)
- Not all defects in DNA damage repair are (currently) targetable
- The <u>results</u> of some defects are targetable (e.g. MSI, TMB)
- The process of some defects are targetable (e.g. HRD)
- Current assays are largely measuring results, not process
- Dynamic measurement of process may maximize benefit of certain treatments



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