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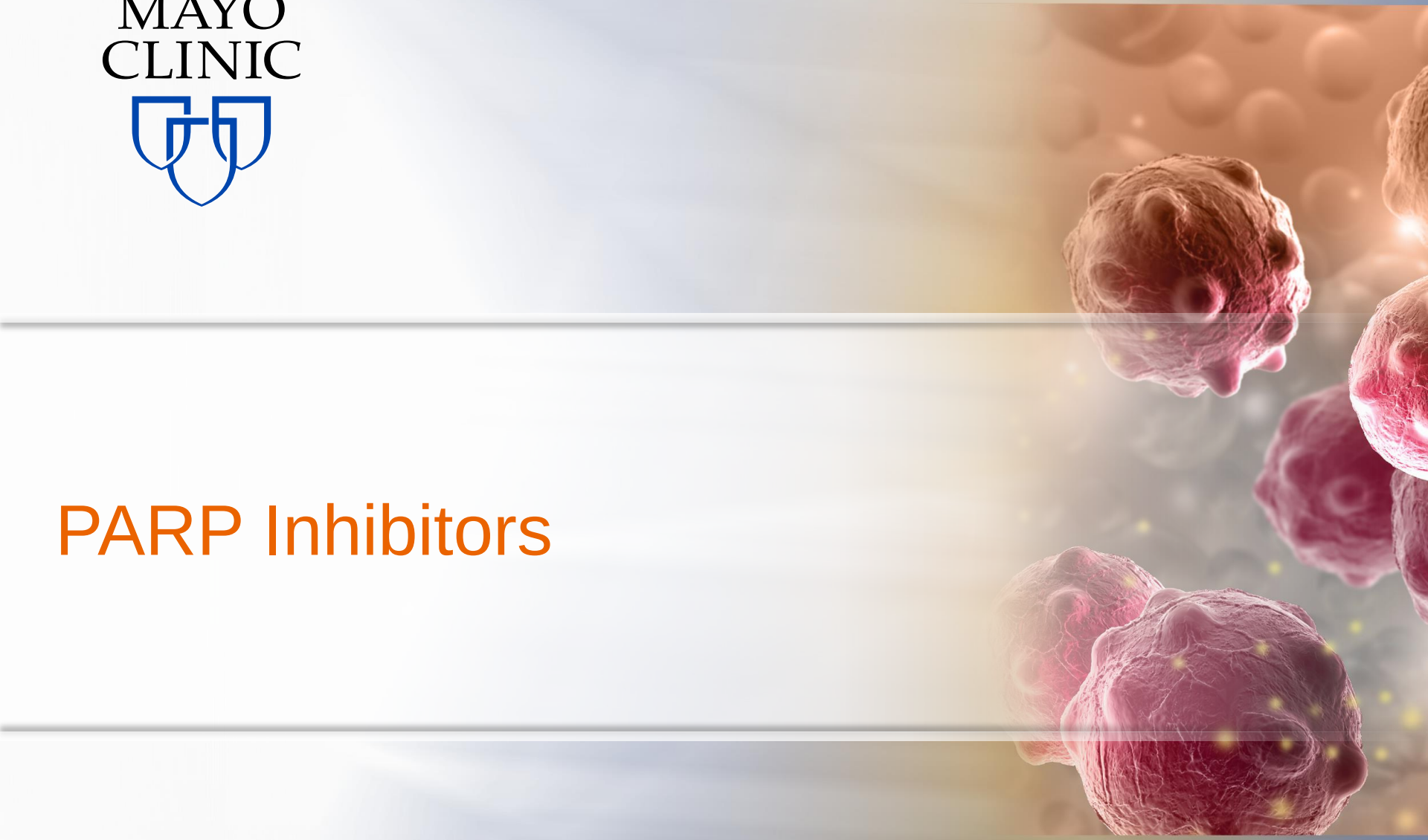

PARP Inhibitors

Discussion points

- What are PARP inhibitors?
- How are they used?
- How do I know if they are right for me?
- What are some common side effects?

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What are PARP inhibitors?

- A medication that blocks an enzyme in cells called poly-ADP- ribose polymerase (PARP)
- PARP is a protein that helps cells repair DNA damage
  - Plays role in the base excision repair pathway
  - If inhibited, leads to build up of double strand DNA breaks in the cells
  - The cells will try to use a different DNA repair pathway to fix that damage (the homologous recombination (HR) pathway)

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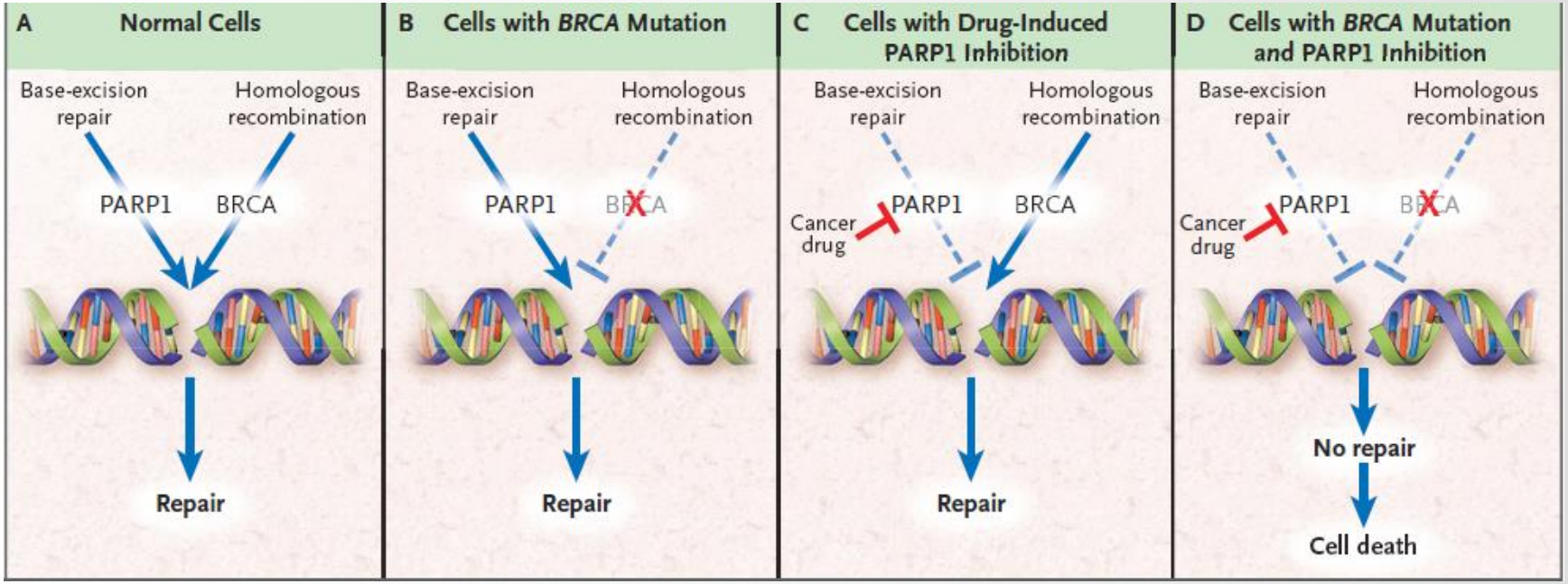
What are PARP inhibitors?



Igelhart JD and Silver DP. NEJM 2009

Why do they work better in some tumors?

- Depends on genetics
  - BRCA1/ BRCA2 mutations
    - These mutations lead to difficulty in repairing DNA damage
      - HR pathway is not working well
    - PARP inhibitors enhance that difficulty
    - Can be a germline (inherited) mutation OR a somatic (tumor only) mutation
  - Other changes in DNA repair that can play a role as well

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Why do they work better in some tumors?

- Other genetic changes
  - Other proteins in the HR pathway
    - Does the tumor have any defects in the HR pathway?
      - Homologous Recombination Deficiency (HRD) score
        - Positive score- pathway is not working completely (defect present)
        - Negative score- no defects in the pathway are noted
    - Discuss the testing and results with your cancer care team

What does that mean for me?

- BRCA1/2 mutation
  - On average, the largest improvement in time to disease recurrence
  - These tumors are also HRD positive
- HRD positive
  - If it is not due to a BRCA mutation, there is still improvement, but usually a bit less than with a BRCA mutation
- HRD negative
  - Least impact since the repair pathway is likely working

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When are they used?

- Can be used as a maintenance therapy and as a treatment
- There is FDA approval for PARP maintenance therapy in front line and recurrence setting
- Now they tend to be used early as a maintenance therapy
  - If the tumor is platinum “sensitive”
    - Tumor has decreased in size after treatment with platinum

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Risk/Benefits of Maintenance Therapy

- Benefits
  - May help keep cancer from coming back
  - May slow down cancer growth

- Disadvantages
  - Side effects
  - Treatment cost
  - More doctor visits
  - Limited information on long term side effects and benefits for each individual

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FDA Approved PARP Inhibitors

Lynparza®
olaparib

Zejula™
niraparib
capsules 100 mg

Rubraca®
(rucaparib) tablets

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PARP inhibitors

- Oral medication
- Take once to twice daily

- Some common side effects
  - Nausea
  - Vomiting
  - Appetite changes
  - Fatigue
  - Weakness
  - Changes in blood counts

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PARP Inhibitor Side Effects

- All have a similar side effects, but some are more common and/or more severe in one versus another
- All can cause AML/MDS (blood diseases)
- Talk to your physician as to which may work best for you
  - Individuals react differently
  - No one right answer for everyone
  - Also depends on the clinical situation

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Questions to consider with your team

- How did the tumor respond to the chemotherapy?
- Do I have a germline mutation which makes me more sensitive to this treatment?
- Was my tumor tested for mutations and/or an HRD score? If so, what were the results?
- What can I expect regarding side effects?
- How does this change the frequency of blood tests and visits to the clinic?

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Parting thoughts. . .
PARP Inhibitors

- Can be used as treatment or maintenance
- The genetics of your tumor are important
- Which to use is based on specific indication and discussion with your physician
  - Genetic status
  - Side effects
  - Dosing schedule

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Thank you!