How to improve the treatment of ovarian cancer patients with PARP inhibitors

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Presentation plan

1. My journey in cancer research
2. What is personalized medicine and how does it work?
3. What are PARP inhibitors and why are we using them?
4. A new era of personalized medicine
5. Clinical trials with PARP inhibitor combination therapies

Montreal, Canada

2006-2009	BS – Biology (UQAM)
2009-2011	MS –Metabolism - hepatic steatosis (UQAM - Drs. Mounier and Rassart)
2011-2016	PhD – Galectins in ovarian and prostate cancer (INRS - Dr. St-Pierre)

Houston, Tx

2016-2018 Postdoctoral fellowship
(MDACC - Dr. Mills)

Adaptive response of ovarian cancer cells to targeted therapies

Portland, OR

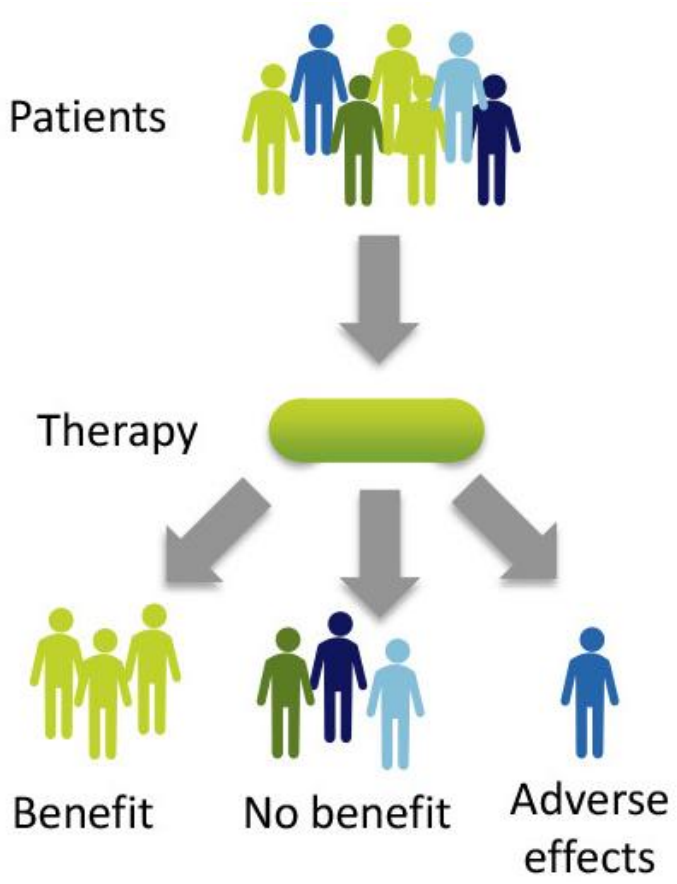
2018-today Postdoctoral fellowship
(OHSU - Dr. Mills)

Adaptive response of ovarian cancer cells to targeted therapies

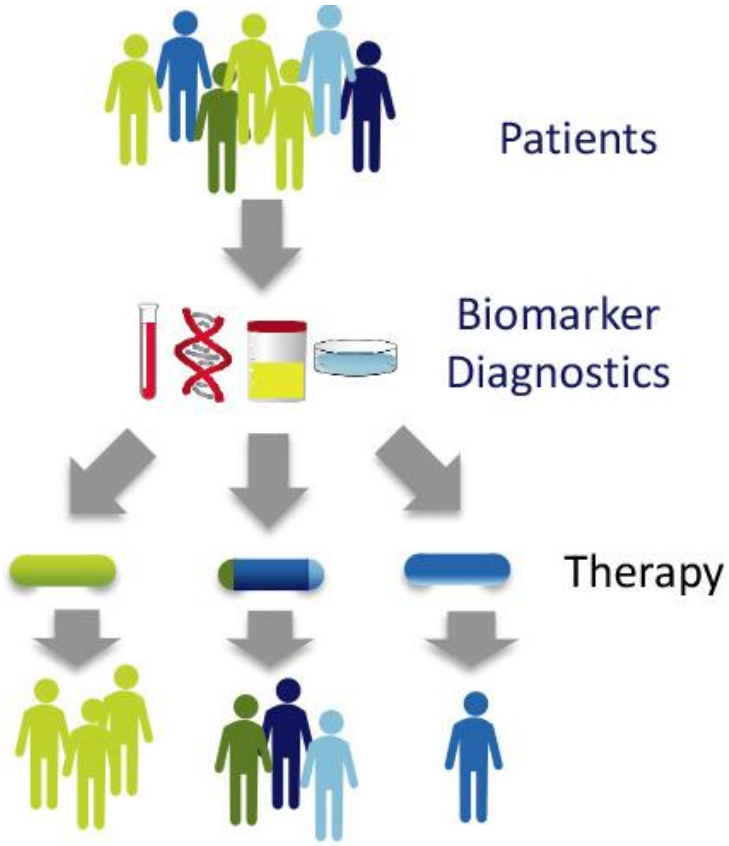
What is personalized medicine?

Patient specific characteristics determine the response to treatment

One drug fits all

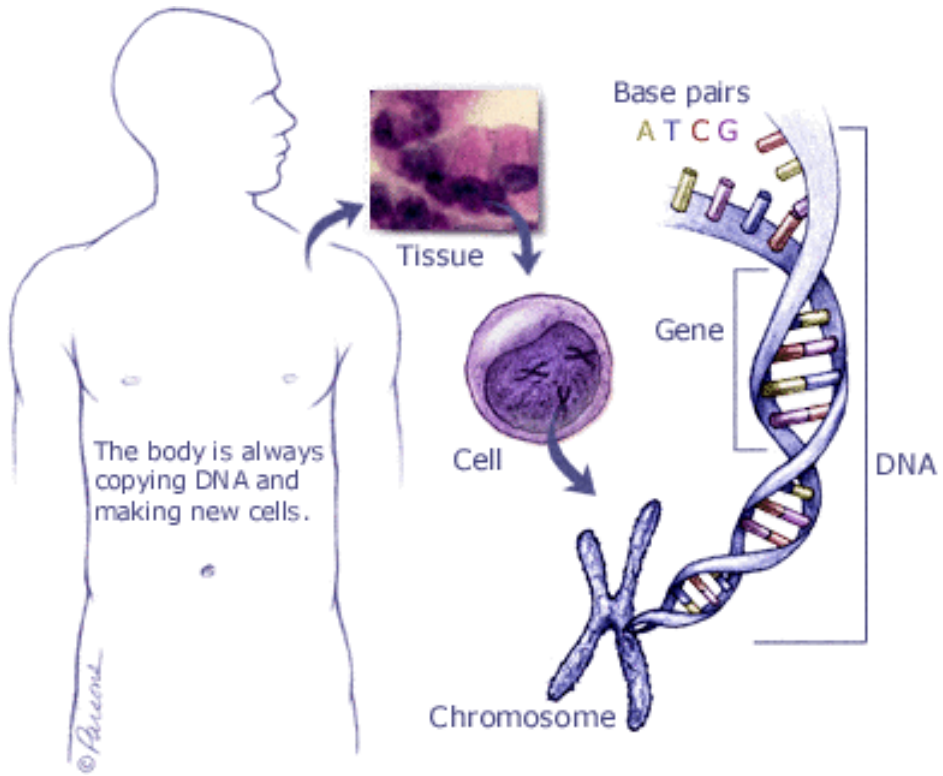


Personalized medicine

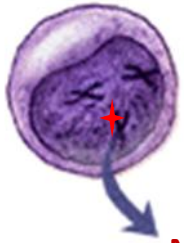


Cancer develops when cells accumulate abnormalities (mutations) in their DNA

The DNA contains the recipe to build any cells from any tissue in our body



Cancer cells have abnormalities in their DNA

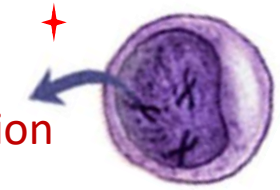


Mutation

- More frequent cell division
- Recruit blood vessels (+ nutrients)
- Trick the immune system

Abnormalities in DNA allow cancer cells to grow and spread around the body

Personalized treatment in ovarian cancer: finding cancer cells' vulnerabilities to cure patients



Gene mutation (examples)	BRCA	CCNE	VEGF	PD-L1	ER
How it helps the tumor	Accumulates genomic abnormalities (Adaptation)	More frequent cell division (Growth)	Ability to recruit blood vessels (nutrients)	Tricks the immune system	More hormone receptors (Growth)
Choice of drug	**Olaparib (PARPi)**	**Chemotherapy (Taxol/Platin)**	**Bevacizumab (VEGFi)**	**Avelumab (PD-L1)** ↓ Not FDA approved yet	**Tamoxifen (anti-estrogen)**

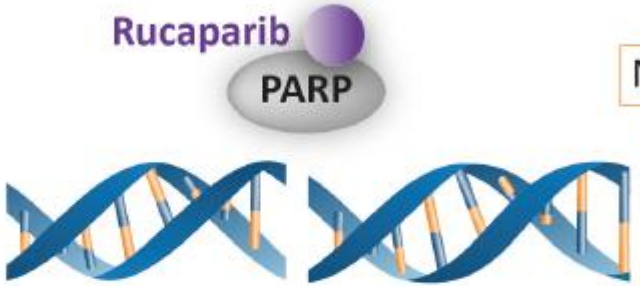
PARP is a protein that helps repair DNA

1. PARP helps repair DNA damage

Rucaparib

PARP inhibitor

2. PARP inhibition leads to more DNA damage



PARP inhibition leads to formation of a double-strand break

Normal cell

Cancer cell

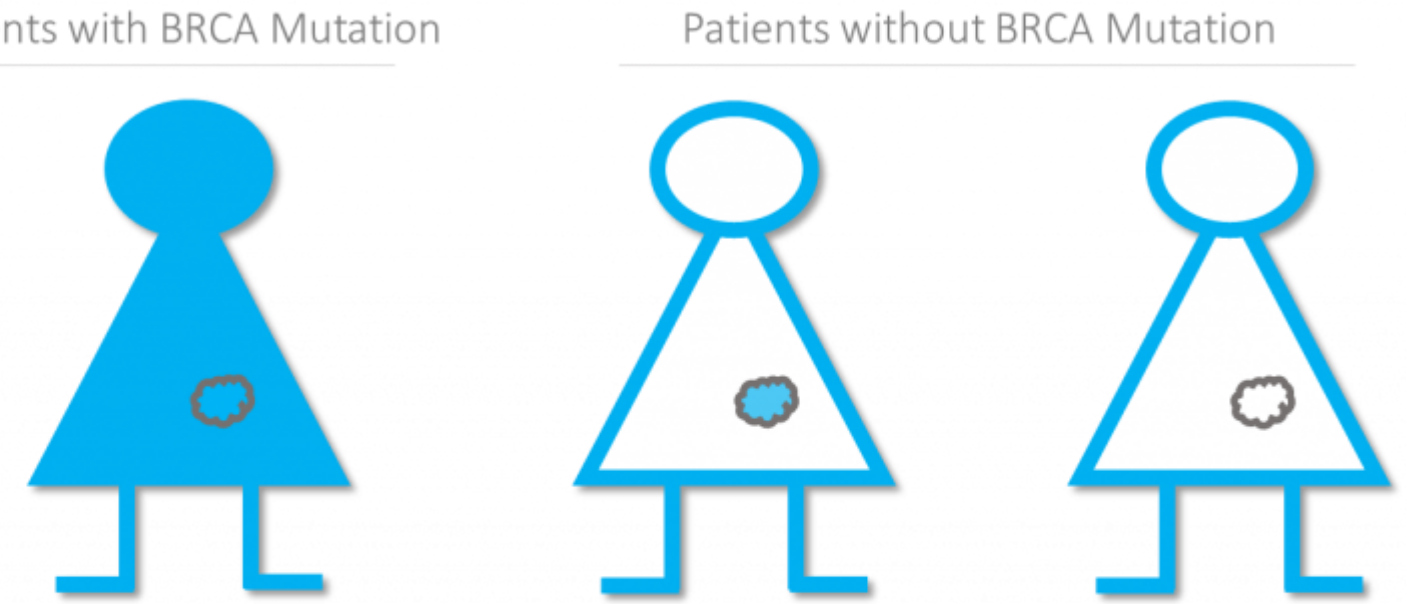
3. Normal cells can repair DNA and survive

Double-strand break is repaired by homologous recombination

Cell survival

4. Cancer cells with defect in DNA repair (BRCA mutation) do not survive

PARP inhibitors kill tumors with defective DNA repair



PARP inhibitors
(Olaparib, Talazoparib, Rucaparib, etc.)

Can we improve the prediction of response to PARPi?

Some patients **with BRCA mutations** respond to PARPi

Some patients **with BRCA mutations** do not respond to PARPi

Some patients **with BRCA mutations** respond to PARPi, but then develop resistance

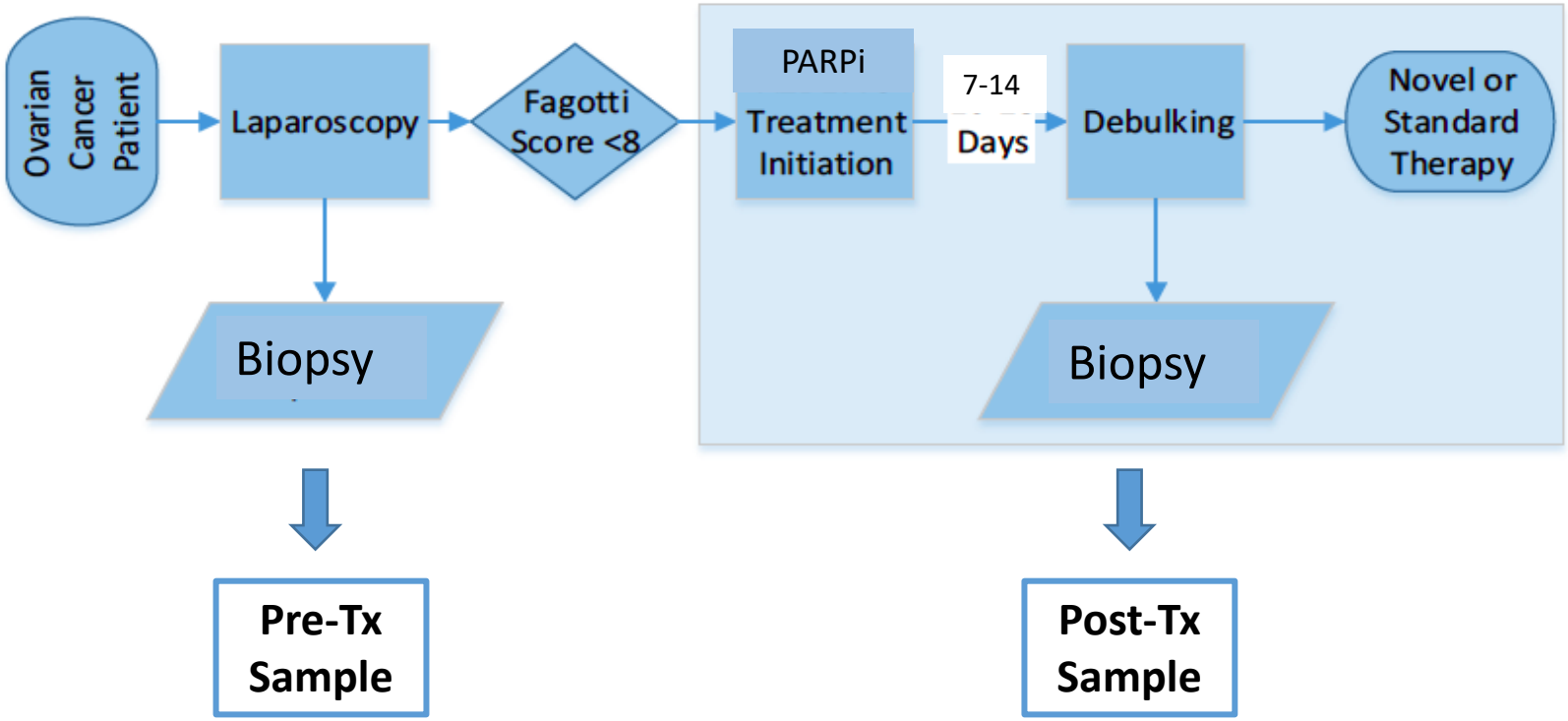
Some patients **without BRCA mutations** respond to PARPi

Some patients **without BRCA mutations** respond to PARPi, but then develop resistance

Some patients **without BRCA mutations** do not respond to PARPi

Can we study how cancer cells respond to PARPi to better direct treatment options?

Window of opportunity trial with ovarian cancer patients to understand how the tumor adapts to PARPi



How is the tumor trying to survive PARP inhibition?

Can we prevent the development of resistance by adding a second drug?

Each patient's tumor has a specific response to PARPi and needs a personalized treatment

Adaptive responses	Patient 1	Patient 2	Patient 3	Treatment options
Immune cells are present but not activated	X	X	X	Immune therapy (PD-L1)
The tumor activates a response to repair DNA damage	X			DNA Damage checkpoint (WEE1, Chk1, ATR inhibitors)
The tumor activates a response to avoid cell death	X		X	Signaling/cell death (MEK, PI3K, Bcl2 inhibitors)
The tumor activates an unexpected response		X		Survival signals (PDGFR inhibitor)

PARPi decision tree

Treat the patient for a short period of time and collect a tumor sample (pre and post-treatment)

1. Is the tumor showing sign of DNA damage repair defect?
   - Yes: PARPi
     - 2. Is it sensitive to treatment?
       - Yes: PARPi
       - No
         - 3. Does it show signs of adaptive responses that can be targeted by a drug?
           - Yes: Combination therapy
           - No: Use other drug
   - No: Use other drug

Clinical trials with PARP inhibitor based combination

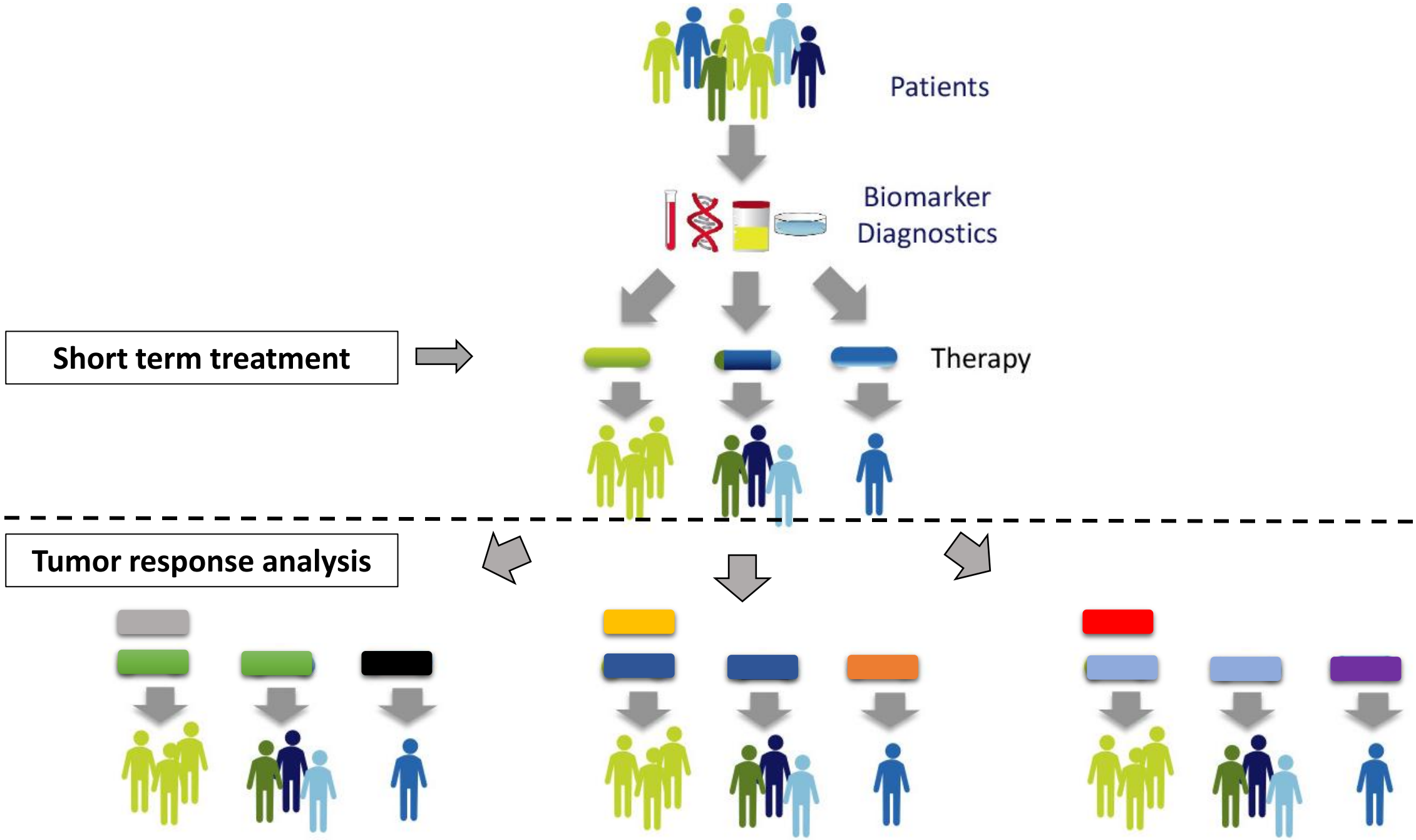
Clinical trials under development for PARP-based combination therapies

Combinational Drug	PARPi	NCT
Carboplatin and Paclitaxel	Veliparib	NCT02470585
Mirvetuximab Soravtansine	Rucaparib	NCT03552471
Lurbinectidine	Olaparib	NCT02684318
Liposomal Doxorubicin	Olaparib	NCT03161132
Floxuridine	Veliparib	NCT01749397
Onalespib	Olaparib	NCT02898207
AZD6738	Olaparib	NCT03462342
Adavosertib	Olaparib	NCT03579316
Bevacizumab	Niraparib	NCT02354131
Bevacizumab	Niraparib	NCT03326193
Bevacizumab	Rucaparib	NCT03462212
Cediranib	Olaparib	NCT02889900
Cediranib	Olaparib	NCT02340611
Cediranib	Olaparib	NCT03278717
Cediranib	Olaparib	NCT02681237
Cediranib	Olaparib	NCT03117933
Cediranib	Olaparib	NCT03314740
Cediranib	Olaparib	NCT02446600
Everolimus	Niraparib	NCT03154281
Copanlisib	Niraparib	NCT03586661
Buparlisib or Alpelisib	Olaparib	NCT01623349
Vistusertib or AZD5363	Olaparib	NCT02208375
TSR-042	Niraparib	NCT03602859

Main class of drugs combined with PARP inhibitors:

1. Immune checkpoint inhibitors (reactivate the immune system)
2. VEGF/VEGFR inhibitors (blocks the blood supply to the tumor)
3. Chemotherapy (Increases the DNA damage)
4. AKT/MEK inhibitors (reduces the survival signals in the cancer cells)
5. DNA damage checkpoint (avoids DNA repair in cancer cells)

Conclusion:
A new era of personalized medicine!


Patients
Biomarker
Diagnostics
Short term treatment
Therapy
Tumor response analysis

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Ruth and Steve Anderson, in honor or Shae Anderson Gerlinger