An update from the SU2C ovarian cancer dream team

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STAND
UP TO
CANCER®
SCIENTIFIC SUMMIT 2017

DNA Repair Therapies for Ovarian Cancer

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Elizabeth Swisher, MD
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STAND UP TO CANCER

Ovarian Cancer Research Fund Alliance

NOCC NATIONAL OVARIAN CANCER COALITION

ADMINISTERED BY AACR American Association for Cancer Research FINDING CURES TOGETHER

SCIENTIFIC PARTNER OF STAND UP TO CANCER

OVARIAN CANCER DREAM TEAM

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UW Medicine
UNIVERSITY OF WASHINGTON MEDICAL CENTER

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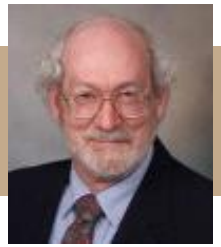
THE UNIVERSITY OF CHICAGO MEDICINE

Maria Jasin, PhD

MEMORIAL SLOAN-KETTERING CANCER CENTER



Scott Kaufmann, MD, PhD

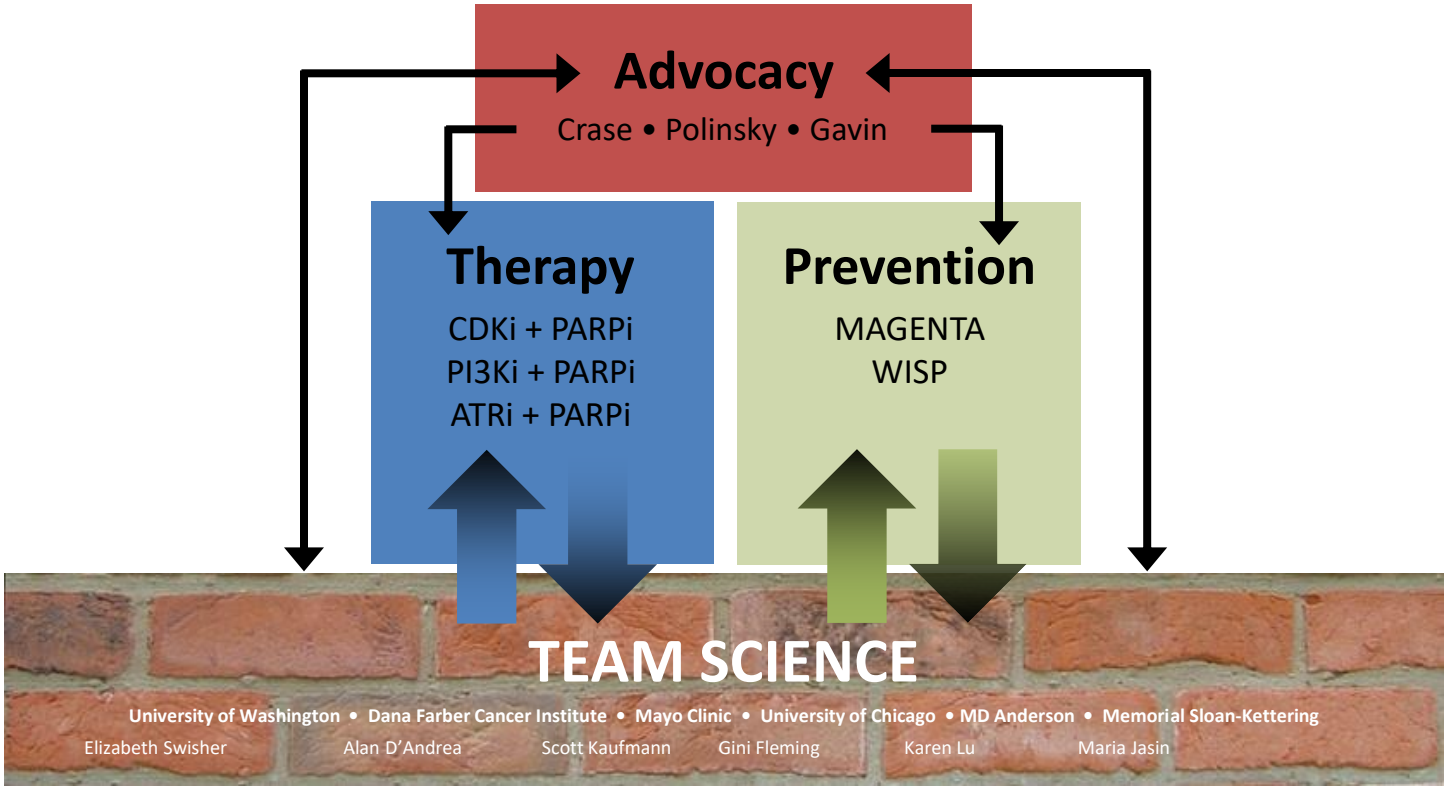
MAYO CLINIC

Karen Lu, MD

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

DNA Repair Dream Team

Impacting Ovarian Cancer Mortality Through Novel Therapies and Prevention



Aim 1: Basic Science

Mechanisms of Sensitivity and Resistance to PARPi

Aim 2: Clinical trials with novel therapies

Novel Drug Combinations to Extend PARPi Use

Aim 3: Clinical trials

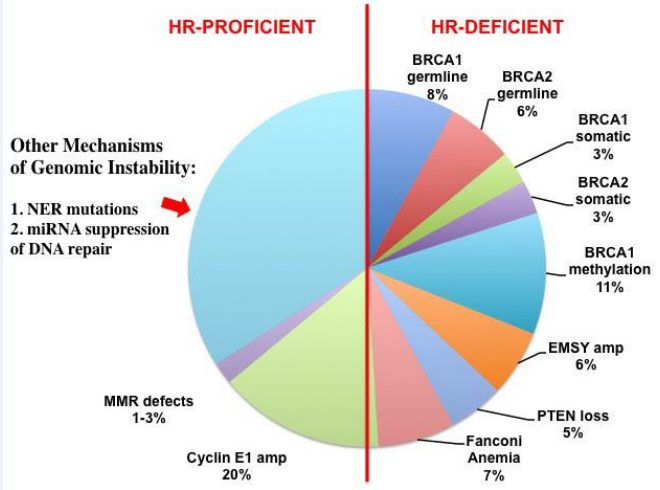
OC Risk Assessment and Prevention

Aim 1

Mechanisms of Sensitivity and Resistance to PARPi

Rationale:

- 50% of Serous OC have DNA Repair (HR) Deficiency
- Olaparib approved for OC with BRCA1/2 mutations
- Need for identifying additional OC with PARPi sensitivity
- Need to identify mutations in other genes which cause OC



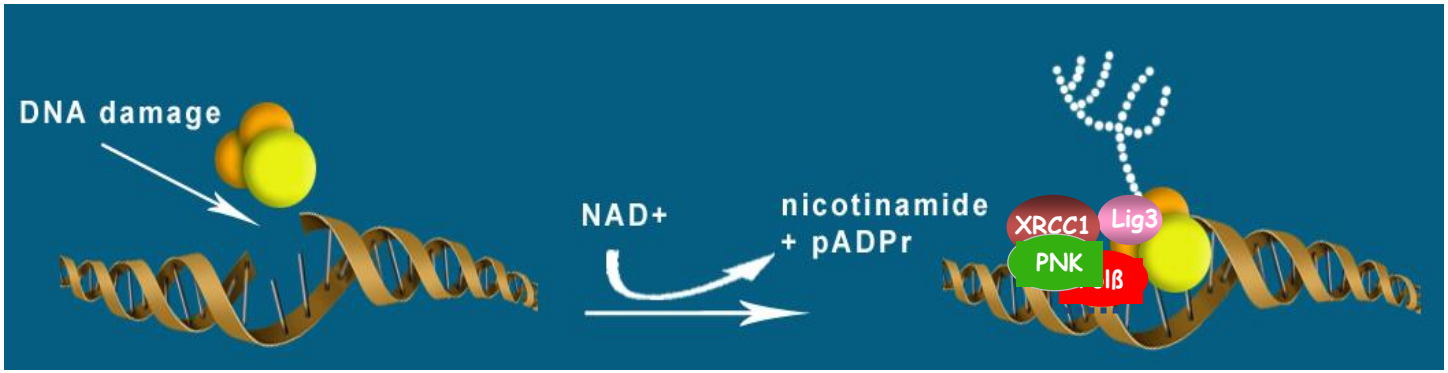
Poly (ADP-ribose) polymerase (PARP)

An enzyme Involved in DNA repair

Binds directly to DNA damage

Recruits other proteins to the site of DNA repair

Ovarian Tumors are Hyperdependent on PARP

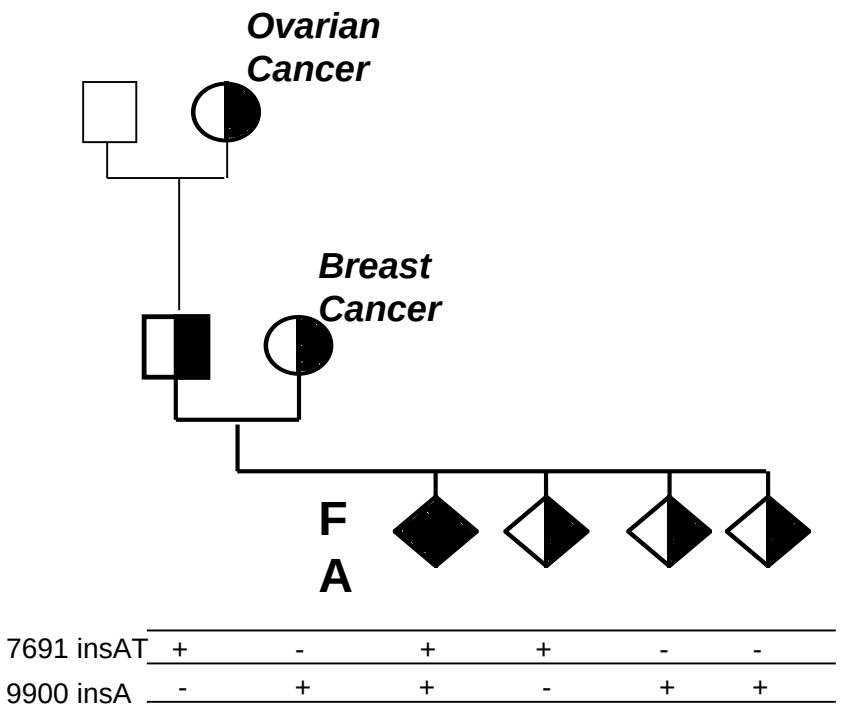


Modified from Alan Ashworth

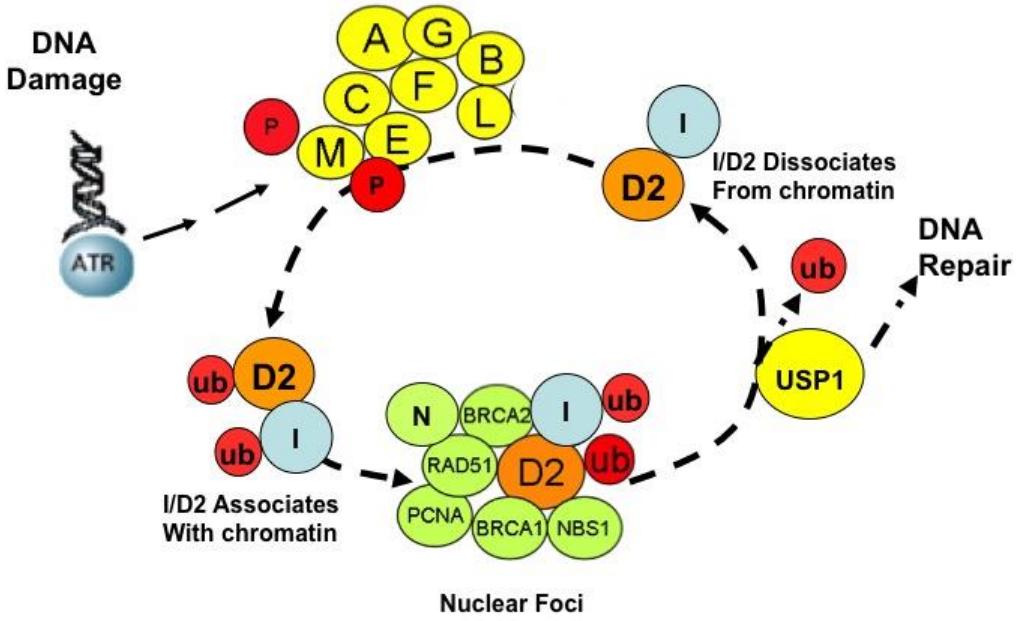
Fanconi Anemia
RESEARCH FUND, INC.

www.fanconi.org

BRCA2 is a Fanconi Anemia Gene



Discovery of the Fanconi Anemia/BRCA DNA Repair Pathway



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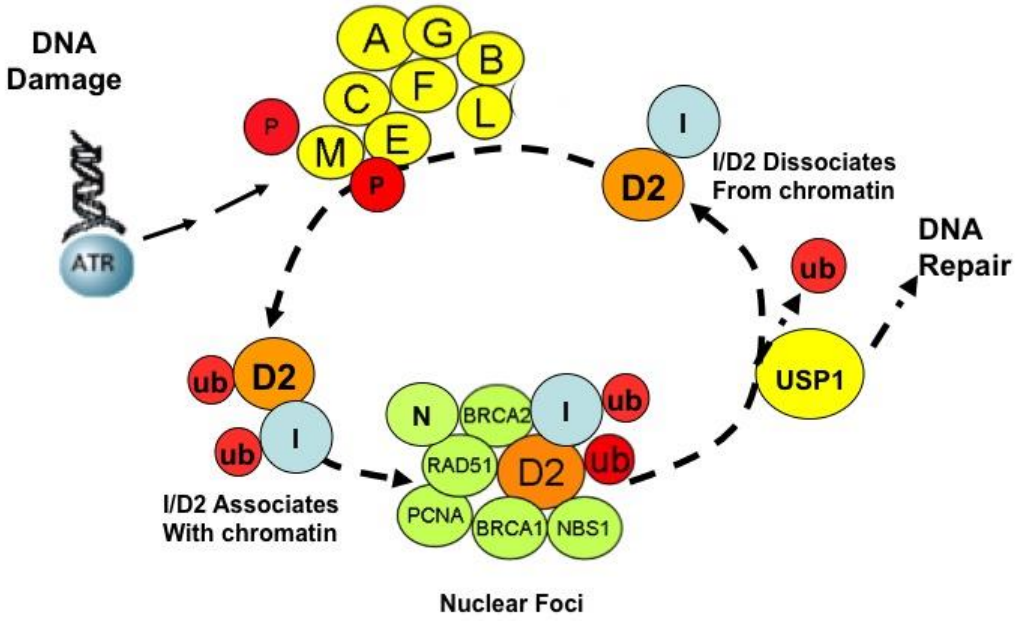

Mutations in any of these 20 genes:

1) Identify Tumors which will respond to a PARPi
2) Identify Women at risk of developing OvCancer

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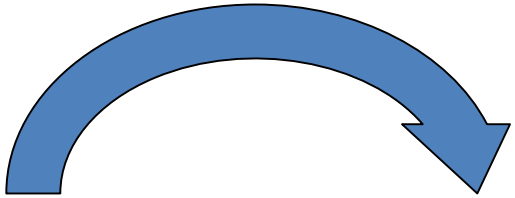
Aim 2 objective:
Extend PARP inhibitor efficacy to HR-proficient tumors

Agents that inhibit HR



HR-PROFICIENT → HR-DEFICIENT

\+

PARP - Inhibitor

PARPi + CDKi – Aim 2A

PARPi + PI3Ki – Aim 2B

PARPi + ATRi – Aim 2C

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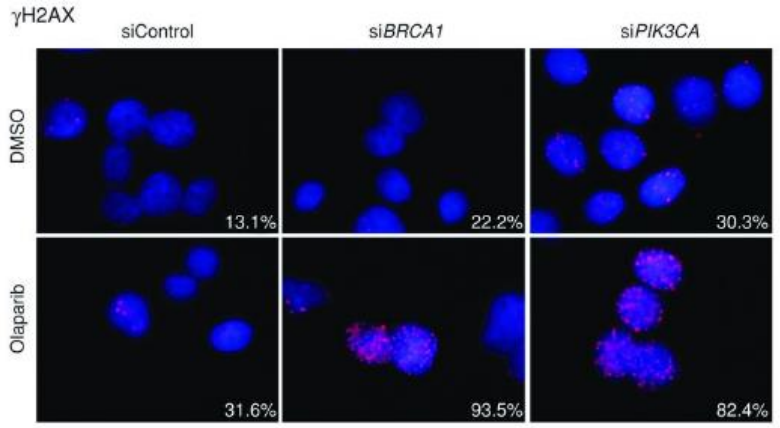
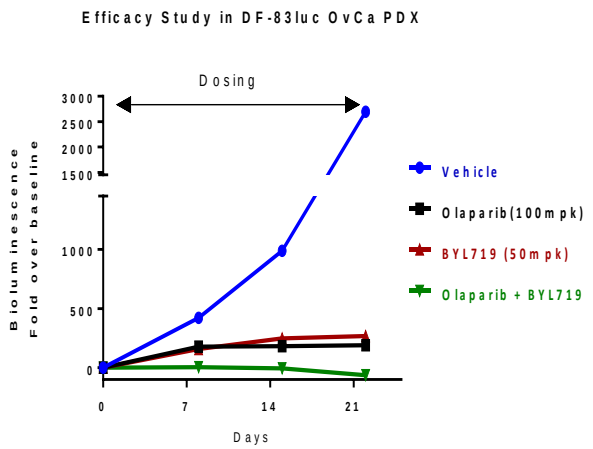
PARPi + PI3Ki – Aim 2B
Preclinical

Mouse Models demonstrate that a PARP inhibitor and a PI3K inhibitor are synertistic





Ibrahim *et al*. Cancer Discov 2012, Juvekar *et al. Cancer Discov* 2012, Rehman *et al. Cancer Discov* 2012

Wulf G, Liu J, Palakurthi S, Matulonis U

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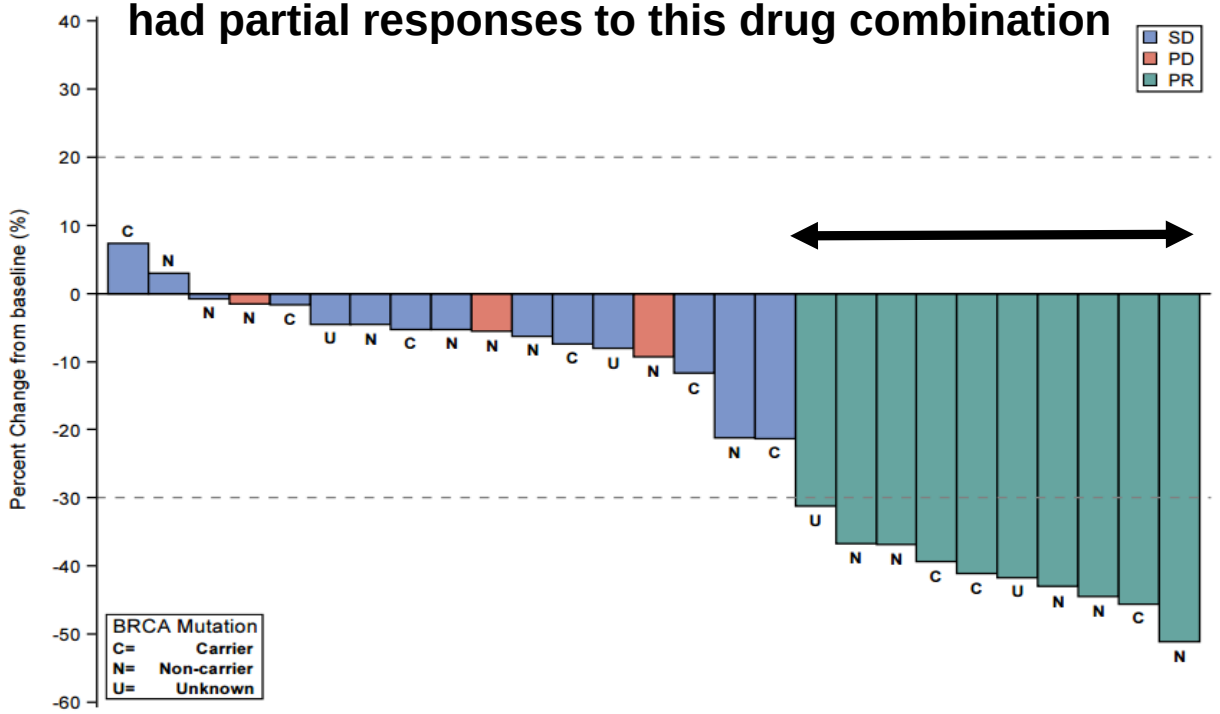
PARPi + PI3Ki – Aim 2B
Phase 1

10 out of 27 patients with relapsed OC had partial responses to this drug combination

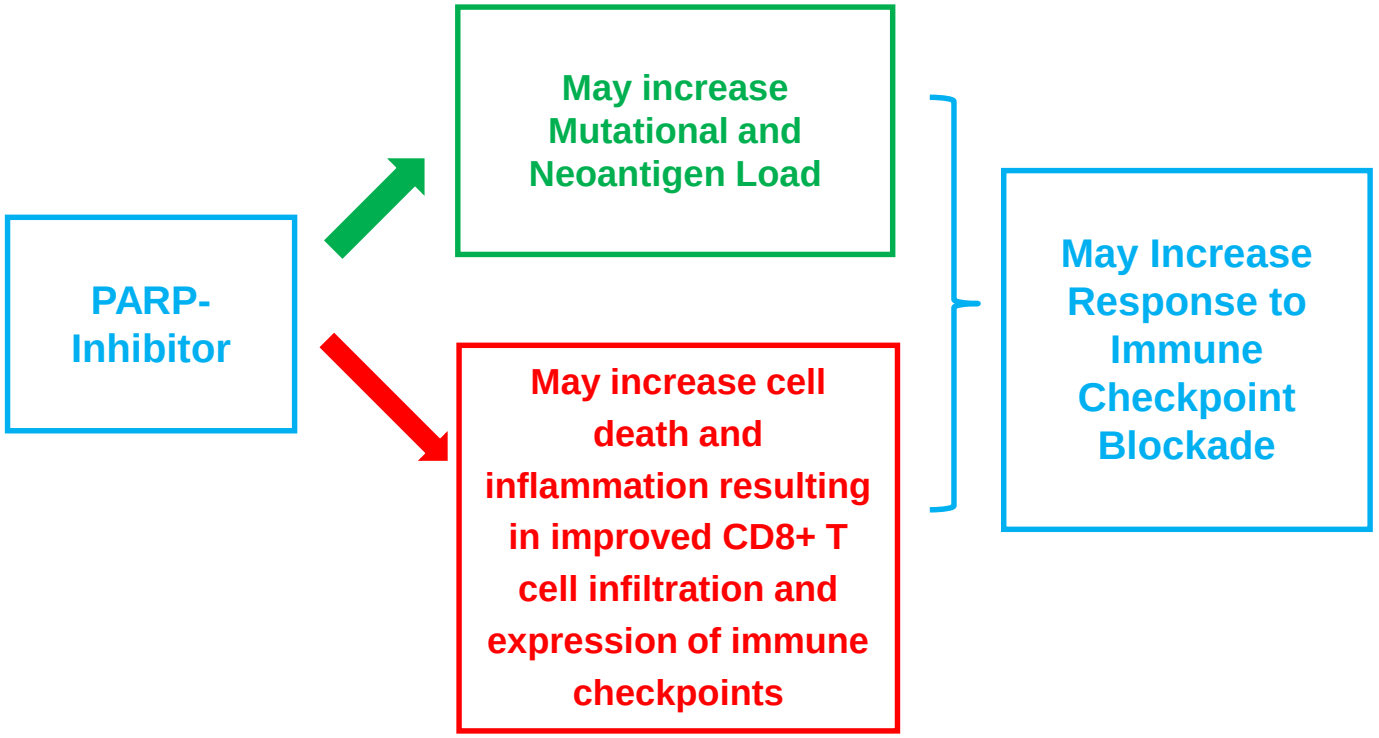


*** 3 patients were excluded due to missing lesion diameters at baseline and follow up**

New Clinical Trial Added to SU2C Portfolio:

Niraparib + Pembrolizumab (NCT02657889)

(New Catalyst Program at SU2C)



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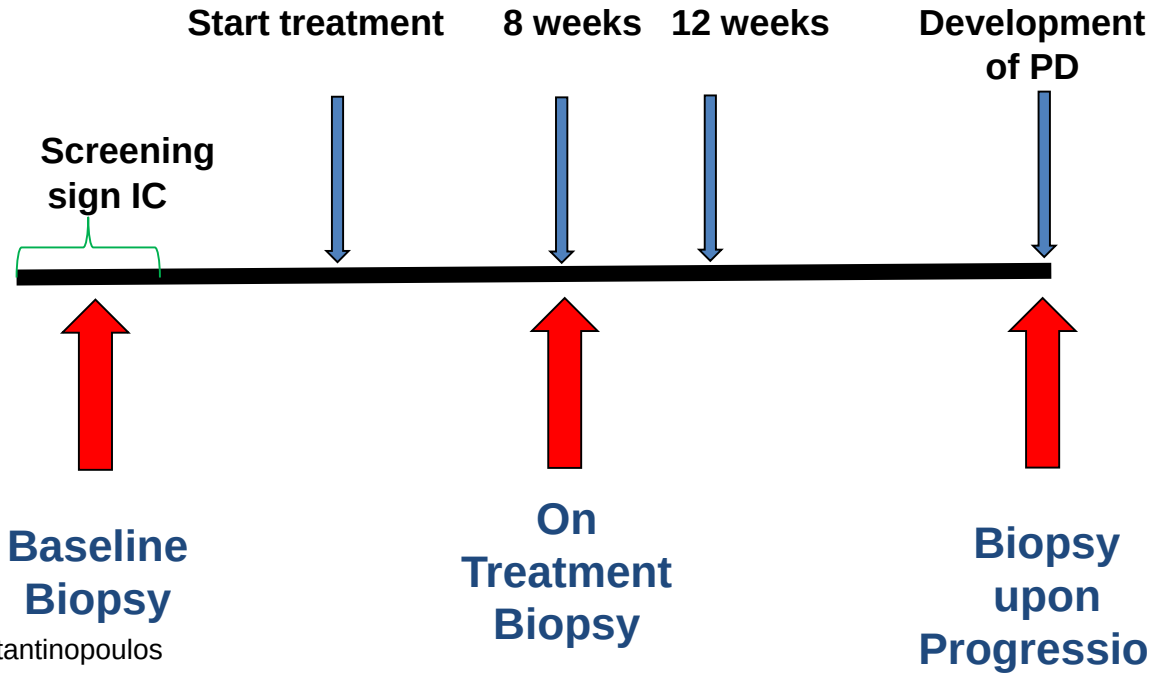
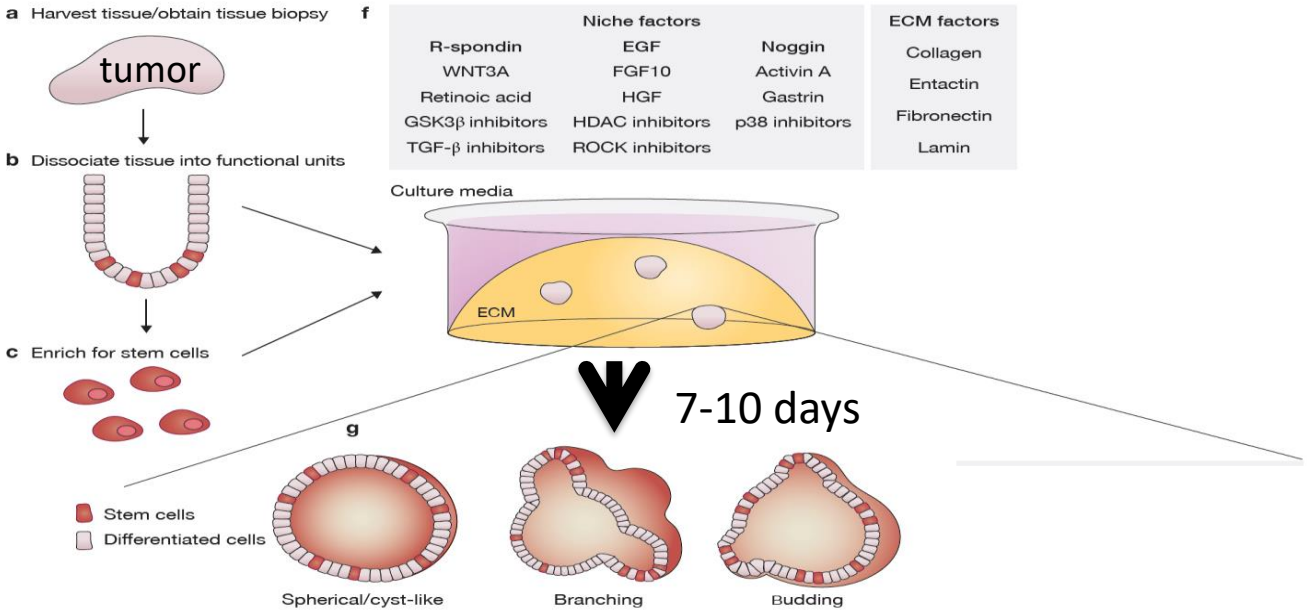
PARPi + immune checkpoint blockade
Catalyst project

Phase 1/2 Trial of Niraparib with Pembrolizumab in Recurrent Ovarian or TN-Breast Cancer

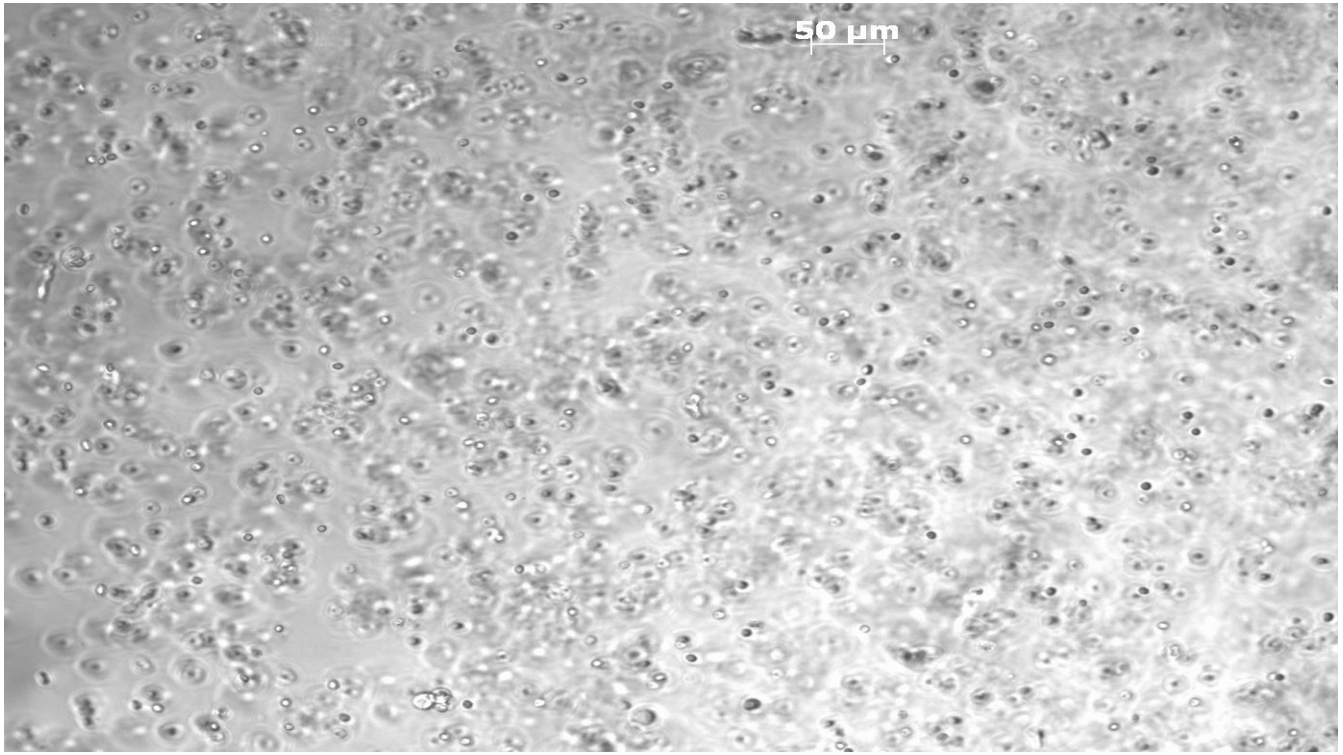


P. Konstantinopoulos

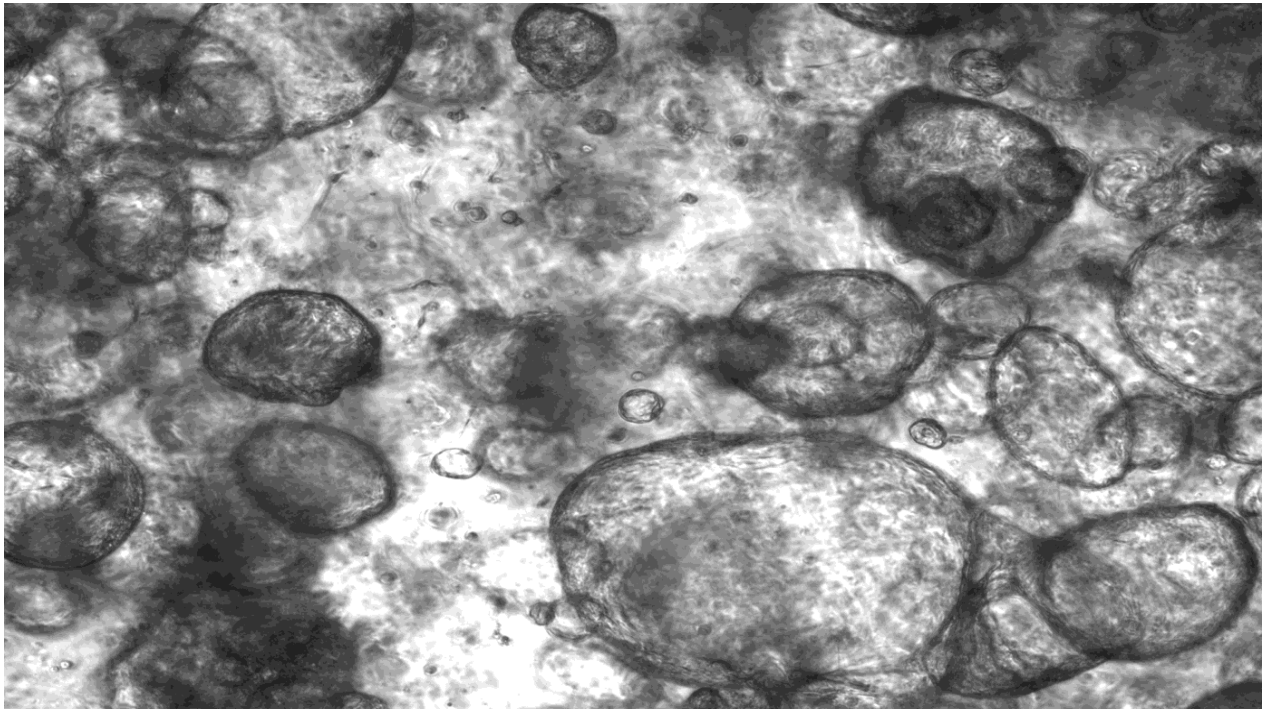
Importance of Functional Tests in Predicting PARPi Resistance: Generation of Ovarian Cancer Organoid Cultures



Fresh Ovarian Tumor Cells on DAY 1



High Grade Serous Ovarian Tumor Organoids-Day 7



These organoids (microtumors) can be directly tested for their sensitivity to new drugs

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Mechanisms of Sensitivity and Resistance to PARPi

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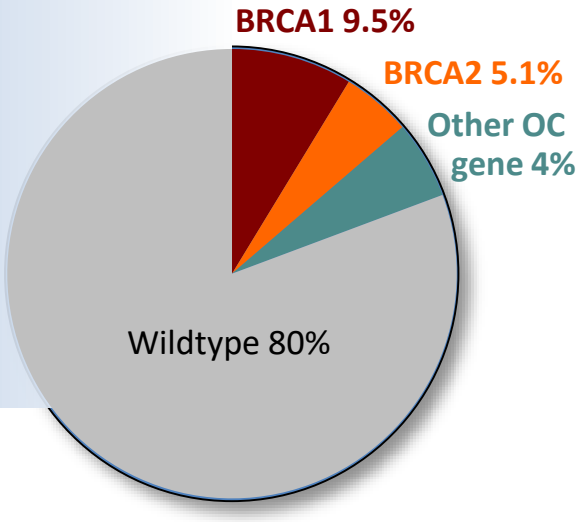
OC Risk Assessment and Prevention

Aim 3

OC Risk Assessment and Prevention

Rationale:

- 20% of OC caused by germline mutations in OC genes
- RRSO effective at decreasing OC mortality in high-risk women
- Genetic testing underutilized
- Not all women willing to undergo RRSO prior to menopause



(*Walsh et al, PNAS, 2011*)

Defining OC Gene Risk → Genetic Risk Assessment → Surgical Prevention

Aim 3

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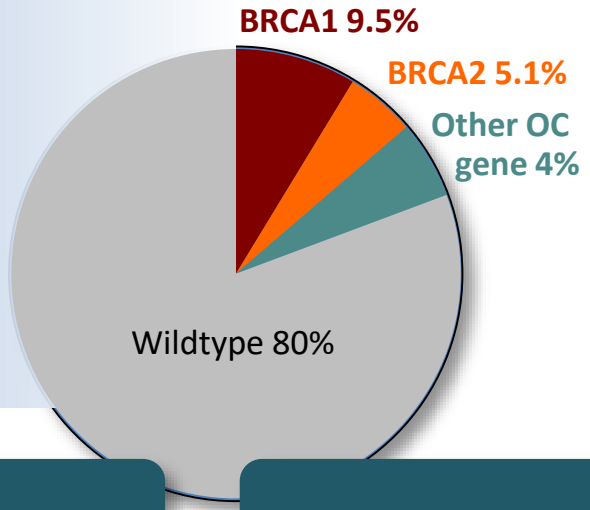

Aim 3A | **Aim 3B MAGENTA** | **Aim 3C WISP**

Defining OC Gene Risk → Genetic Risk Assessment → Surgical Prevention

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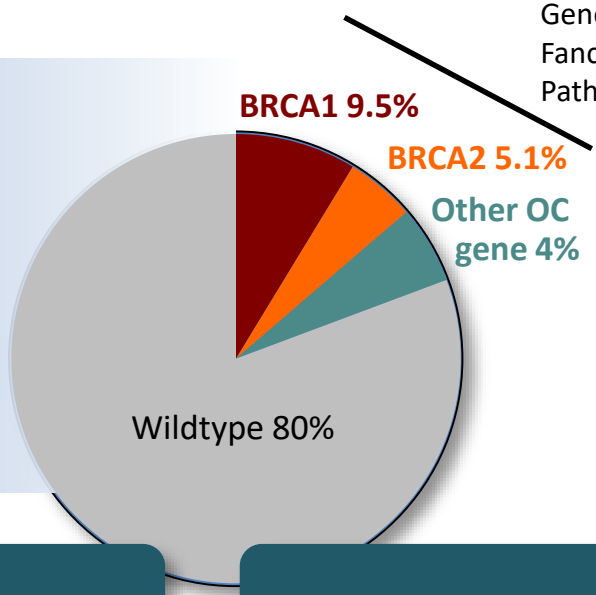


Aim 3A | **Aim 3B MAGENTA** | **Aim 3C WISP**

Defining OC Gene Risk → Genetic Risk Assessment → Surgical Prevention

Aim 3A: Defining Ovarian Cancer Gene Risk

Aim 3A: Case/control evaluation for gene discovery and to determine risk associated with OC susceptibility genes

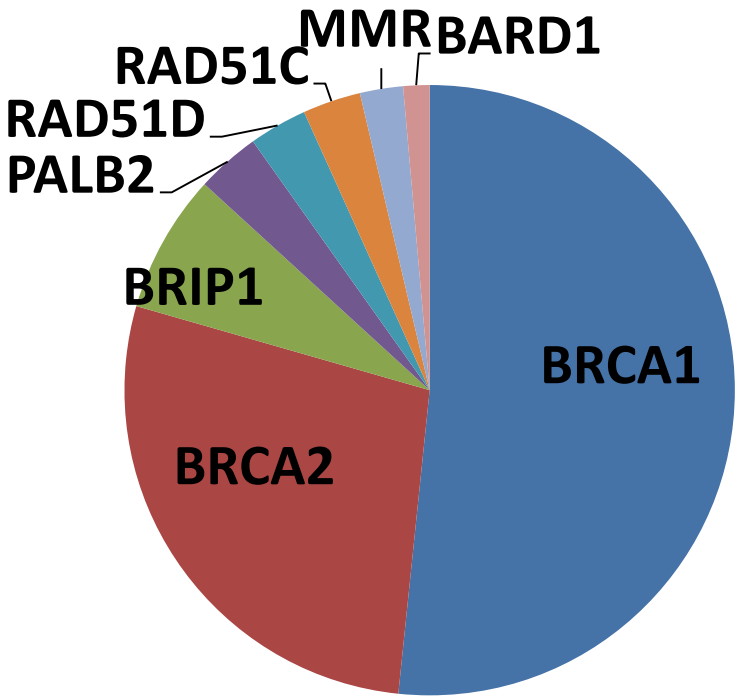
- Increased OC patients sequenced (2221 patients to date)
- No good publically available control population
- Sequenced 10,000 cancer free women from WHI for breast and ovarian cancer susceptibility genes
- Created Flossies database for public access
  - URL: https://whi.color.com/

BRCA1 and *BRCA2*

Important DNA Repair Genes

- 16% of ovarian cancer is caused by inherited mutations in BRCA1 and BRCA2
- BRCA1 mutations: 40% lifetime risk of OC
- BRCA2 mutations: 20% lifetime risk of OC
- 50–80% lifetime risk of breast cancer
- Olaparib is a PARP inhibitor approved for recurrent OC with BRCA1/2 mutations (after 3 previous lines of treatment)

1/5 of Inherited Mutations for OC Are in Genes Other than *BRCA1* or *BRCA2*



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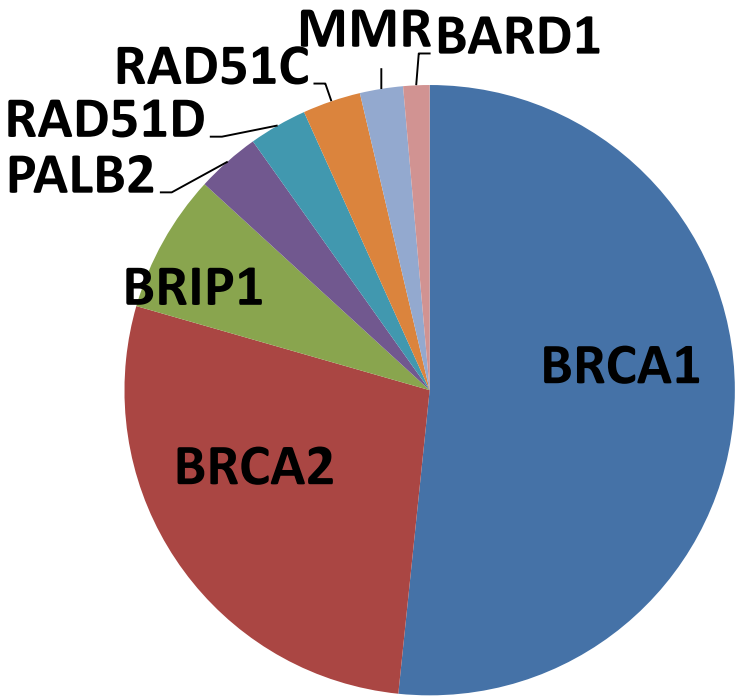


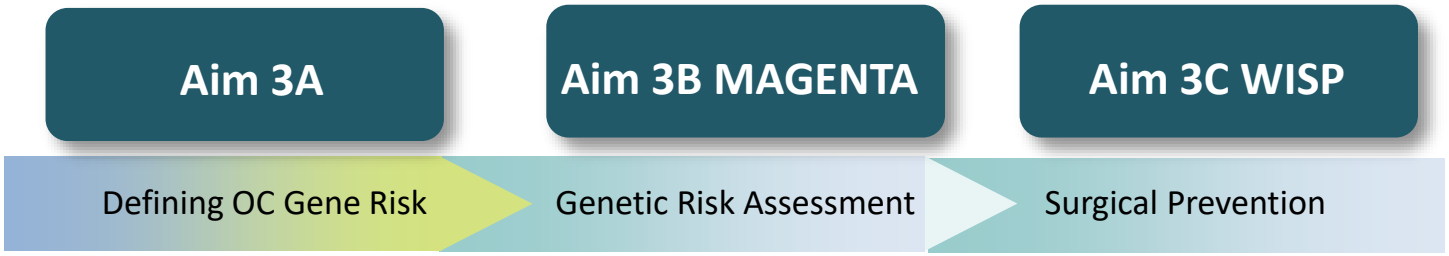
These are other Genes in the Fanconi Anemia/BRCA Pathway

A Family Gift

- **All women with ovarian cancer should have genetic testing**

Why should all women with ovarian cancer have Genetic Testing?

- Identifies cancer risk to other organs
- Allows other family members to know they are at risk
- 1/3 of inherited OC occurs in women with no family history of breast or ovarian cancer
- 40% of inherited OC occurs in women who are not younger than typical.
- Knowing your genetic status may be important for choosing therapy


Aim 3A
Aim 3B MAGENTA
Aim 3C WISP
Defining OC Gene Risk
Genetic Risk Assessment
Surgical Prevention

making genetic testing accessible

The study of genetic testing from your living room.
A Stand Up to Cancer/SU2C initiative at MD Anderson

GOAL

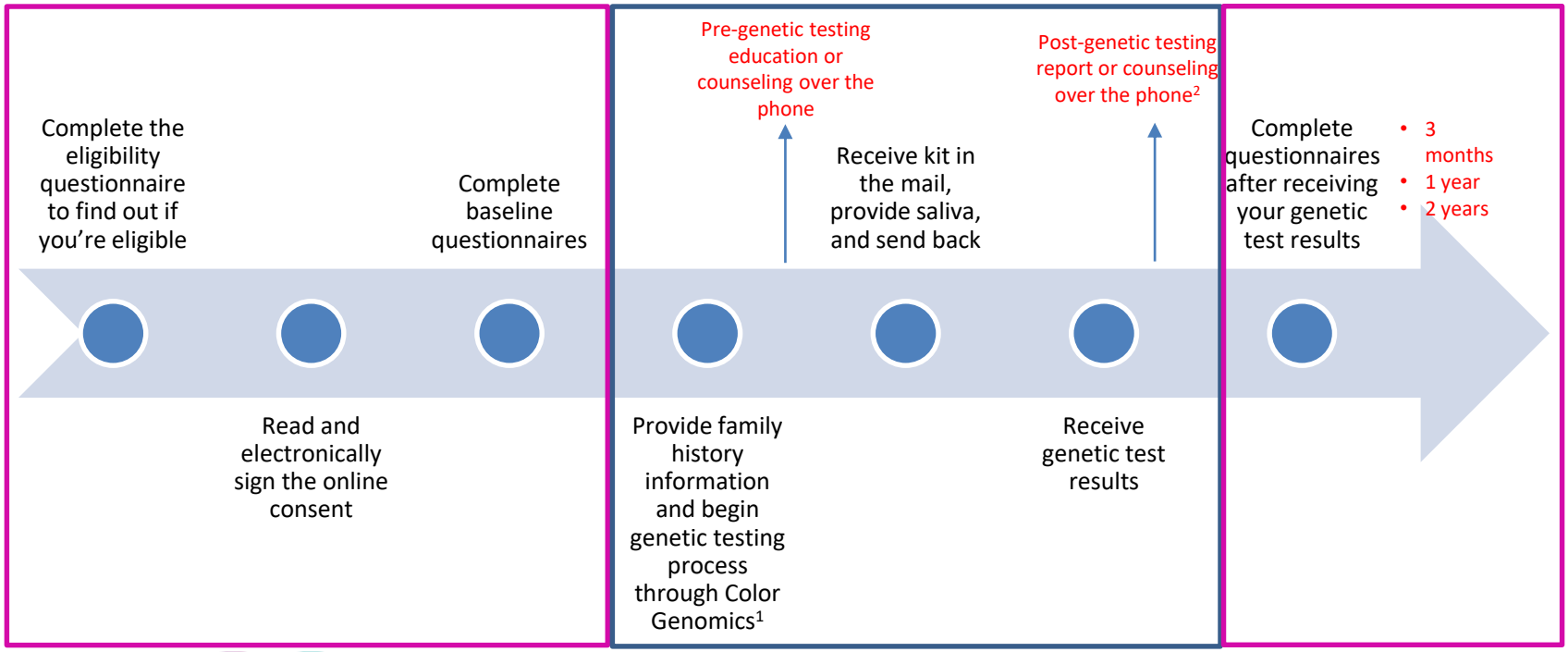
Assess how well we can deliver genetic testing for breast and ovarian cancer risk to women in their living room

TARGET Population:

- Women without ovarian cancer
- Age ≥30
- No prior genetic testing

Personal history BC or family history BC/OC (Group 1, N=2,250)	Relative with known mutation Cascade testing (Group 2, N=750)

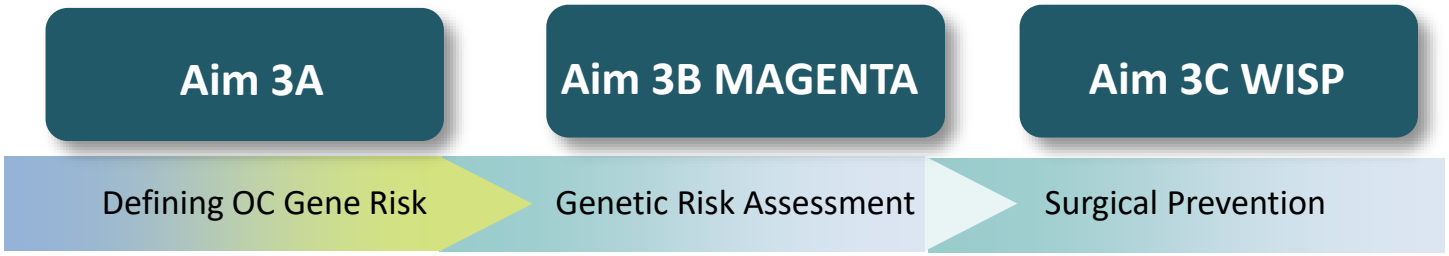
MAGENTA Study Timeline



[1] Color Genomics owns and operates a CLIA licensed and CAP-accredited laboratory in California, U.S.A. that will be performing the genetic testing.
[2]All participants with a positive test result will receive genetic counseling over the phone

Challenges

- Regulatory:
- Online Consent
  - 1st study at MD Anderson that uses online consent
  - Distress Plan
  - How can you provide support to someone who is distressed over the results they are receiving?
    - Setting up triggers through the questionnaires
- Legal:
- Ordering physician: Practicing medicine across state lines
- Genetic counseling: Licensing
  - Using genetic counselors from Color Genomics


Aim 3A
Aim 3B MAGENTA
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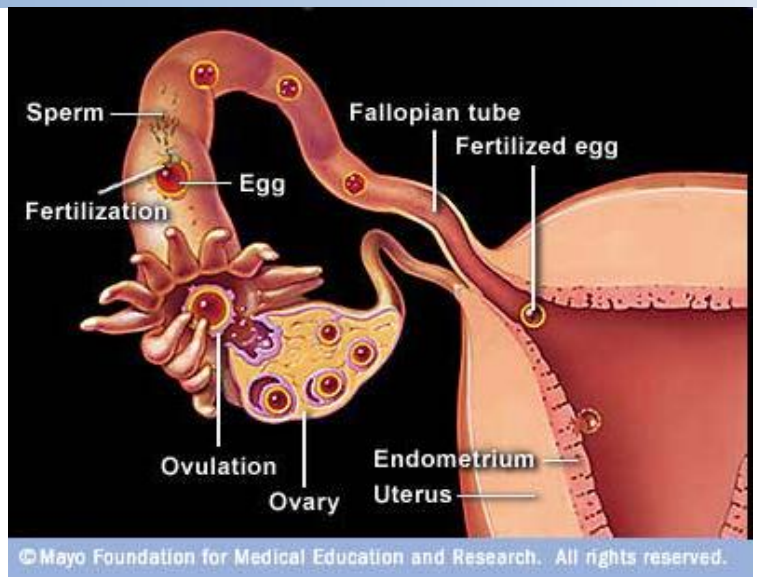
The Tubal Hypothesis

A majority of serous ovarian and peritoneal carcinomas are actually seeded from cancer cells from the tubal epithelium



WISP

Inclusion Criteria:

- Age 30–50
- Premenopausal
- Known mutation in OC gene

Scripted counseling on recommended age for oophorectomy

Interval Salpingectomy

Delayed Oophorectomy

RRSO

PRIMARY Outcome: Sexual Function (FSFI)

SECONDARY Outcomes:

- Vasomotor symptoms (MRS)
- Psychological symptoms (HADS)
- Pathological results (TIC, carcinoma)

Study Design

270 evaluable patients recruited into one of two arms

- –Arm 1: interval salpingectomy with delayed oophorectomy (ISDO) with approximately 135 patients
- – Arm 2: risk-reducing salpingo-oophorectomy (RRSO) with approximately 135 patients.

- – Patient self-select arm, but MDs are mandated to recommend RRSO for BRCA1 carriers at age 40 and BRCA2 carriers at 45, if choose to delay BSO, then must reiterate that recommendation yearly.

RECOMMENDATIONS FOR HIGH-RISK WOMEN

Women at increased risk of ovarian cancer based on a genetic mutation are recommended to undergo removal of the fallopian tubes and ovaries (RRSO) by age 40 for BRCA1 and by age 45 for BRCA2.

For gene mutations including MLH1, MSH2, MSH6, PMS2, BRIP1, RAD51C, and RAD51D, there are recommendations to consider RRSO, although age is not specified.

GOAL OF TRIAL

To determine whether interval salpingectomy, followed by delayed oophorectomy (ISDO) can improve sexual functioning and menopausal symptoms compared to standard risk-reducing salpingo-oophorectomy (RRSO).

ELIGIBILITY

Pre-menopausal women between the ages of 30 and 50 with a documented mutation in one of the following eleven (11) ovarian cancer genes: BRCA1, BRCA2, BRIP1, PALB2, RAD51C, RAD51D, BARD1, MSH2, MSH6, MLH1, or PMS2.* (ie, genes in the Fanconi Anemia/BRCA Pathway)

CHOICE 1: RISK-REDUCING SALPINGO- OOPHORECTOMY

The removal of both ovaries and the fallopian tubes

•This is standard of care

•Most effective preventative measure: reduces the

•risk of ovarian cancer by 85-90%

•Can also reduce the risk of breast cancer

•If no personal history of breast cancer, can

•take hormone replacement therapy to reduce menopausal symptoms

•WHAT ARE THE DOWNSIDES?

•Causes menopause, symptoms of which include hot ashes, night sweats, vaginal dryness, mood changes and sleep disturbances

•Premature menopause may also increase the risk of other important health conditions, such as osteoporosis and cardiovascular disease

CHOICE 2: INTERVAL SALPINGECTOMY WITH DELAYED OOPHORECTOMY

The removal of the fallopian tubes, while temporarily
delaying the removal of the ovaries

- Not yet proven to be effective at preventing ovarian cancer
- Retains ovaries, which helps delay the onset of menopause
- Avoiding premature menopause decreases the risk of some health conditions

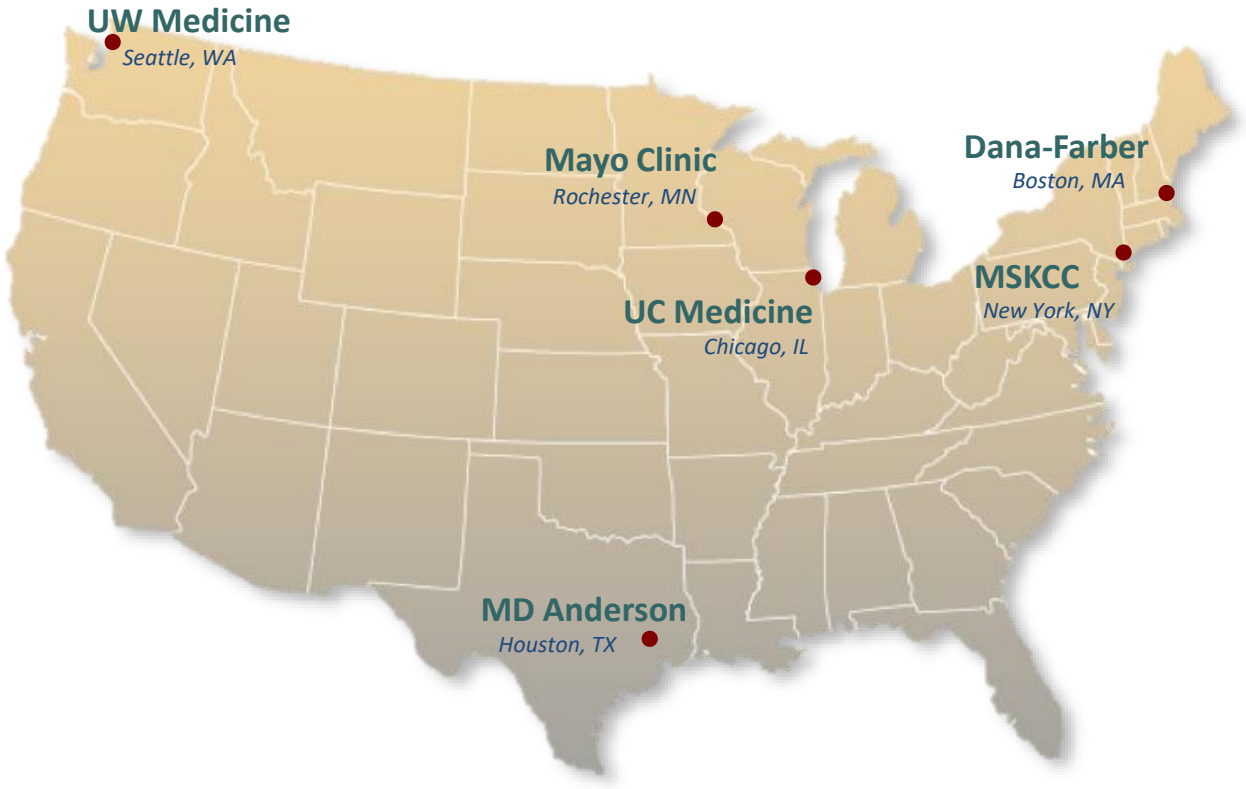
WHAT ARE THE DOWNSIDES?

Research indicates that not all ovarian cancers originate in the fallopian tubes, so this surgery is not as effective in reducing risk as a salpingo-oophorectomy

May develop ovarian cancer

Requires a second surgery to remove the ovaries

Not likely to reduce the risk of breast cancer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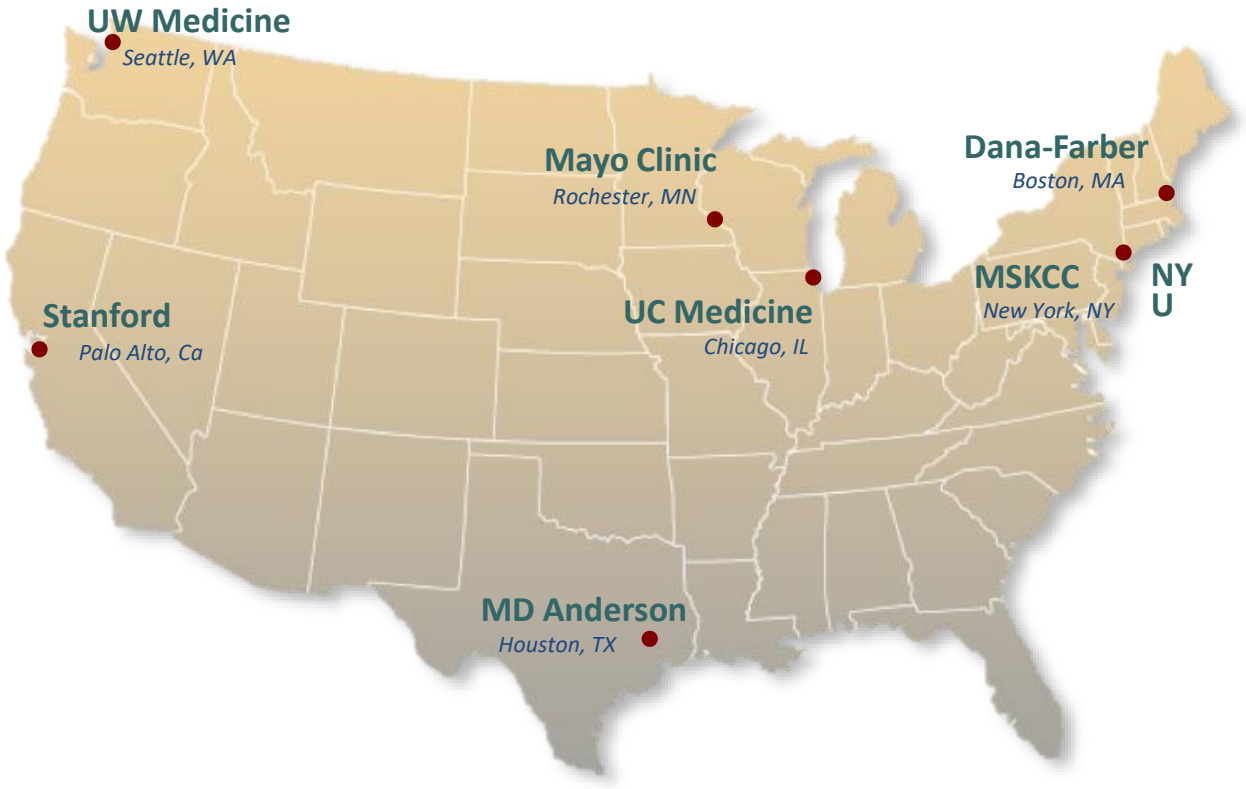
Dana-Farber
Boston, MA
MSKCC
New York, NY
UC Medicine
Chicago, IL
MD Anderson
Houston, TX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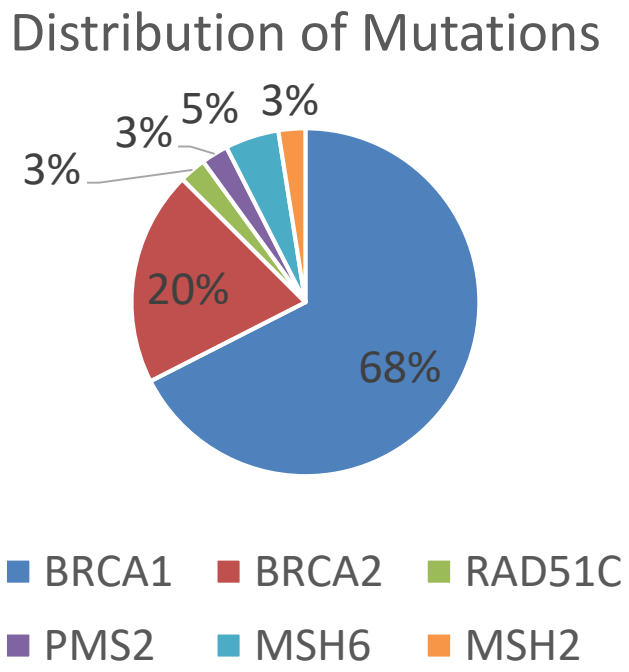
Houston, TX

WISP enrollment to date



Mutation	Number of Patients
BRCA1	27
BRCA2	8
RAD51C	1
PMS2	1
MSH6	2
MSH2	1

DNA Repair Dream Team

Strengths of DNA Repair Dream Team

- Diverse, complementary team of investigators from six world class institutions
- Novel therapeutic interventions for delivering near-term patient benefit
- Potential for reducing OC mortality through prevention
- Application of new basic science mechanisms to DNA repair profiling
- Biopsies from clinically-annotated PARPi trials
- Recent olaparib, rucaparib, niraparib approval
- Industry collaborations
- Committed advocates

UW Medicine
UW SCHOOL OF MEDICINE

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

DANA-FARBER CANCER INSTITUTE

Memorial Sloan Kettering Cancer Center

MAYO CLINIC

THE UNIVERSITY OF CHICAGO

Take home messages

- Defective DNA Repair in OvCA is a fundamental vulnerability of this cancer
- There is a lot of serendipity in science
- Need to support basic and clinical research simultaneously with a wide range of investigators
- Need to focus more on early detection, identification of women at risk, and prevention strategies

Thank You!

- GOAL: Eliminate death and suffering from ovarian cancer
- Requires everyone working together; patients and families, advocates, researchers, medical providers
- Support from Advocacy Community is essential
- Raising awareness
- Supporting research financially
- Enrolling in clinical trials
-
-

DNA Repair Dream Team

Advocates

Jamie Crase

Kathleen Gavin

Deborah Polinsky

Panos Konstantinopoulos
William Barry
Alan D'Andrea

Ursula Matulonis
Geoffrey Shapiro
Giovanni Parmigiani

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Ursula Matulonis, MD
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William Barry, PhD
Giovanni Parmigiani, PhD
Neal Horowitz, MD
Ariana Peralta
Karen Eldridge
Alexandra Feinstein
Don Watson

Elizabeth Swisher, MD
Mary-Claire King, PhD
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Tomas Walsh, PhD
Barbara Norquist, MD
Maria Harrell, PhD
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Kathy Agnew
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Gini Fleming, MD
Phillip Connell, MD
Olufunmilayo Olopade, MD
Anthony Montag, MD
Jane Churpek, MD
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Morgan Whipkey, MD

Maria Jasin, PhD
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John Petrini, PhD
Elizabeth Kass, PhD
Kara Long Roche, MD
Jeanne Carter, PhD
Robert Soslow, MD
Rohit Prakash, PhD
Marcel Hohl, PhD

Karen Lu, MD
Junjie Chen, PhD
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Denise Nebgen, MD, PhD
Anna Yemelyanova, MD
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