Ovarian Cancer
Genetic Testing

Adnan R Munkarah, MD

Chief Clinical Officer, Henry Ford Health System

Professor, Obstetrics & Gynecology

Wayne State University

History

- BRCA and Lynch testing introduced in the 1990s
- Initially reserved for patients with early onset cancers and those with ‘strong family hx’.
- Perceived low rate of mutations in women with gyn cancers
- Presence of mutation does not impact cancer management
- Complexity of testing
- Cost of testing
- Rapidly changing technology

Present

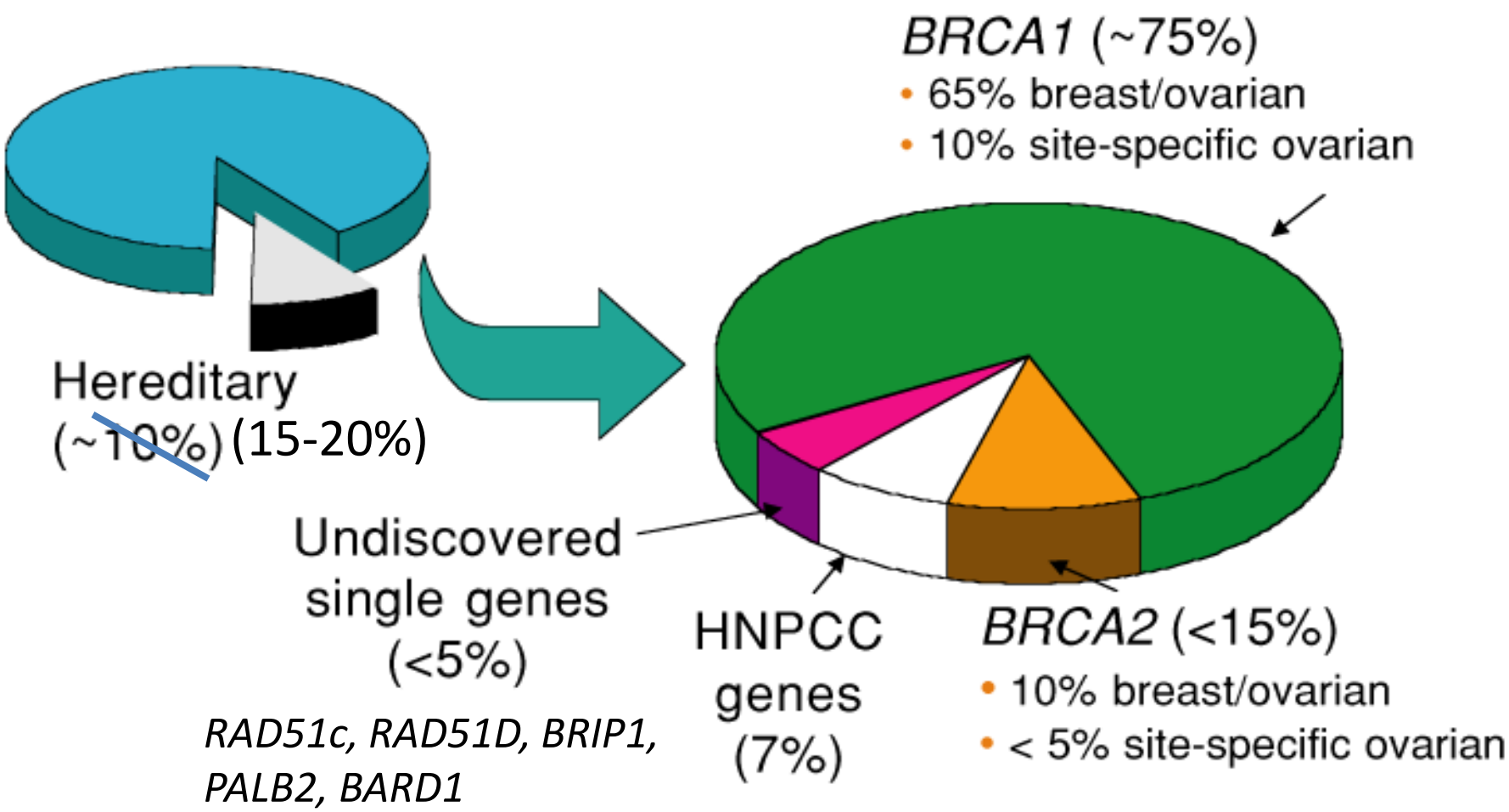
US Preventive task force, SGO, NSGC recommend testing for all women with ovarian, tubal or peritoneal cancer regardless of age or family hx

Genetics
BRCA testing

BRCA Mutation Prevalence
Personal Cancer History

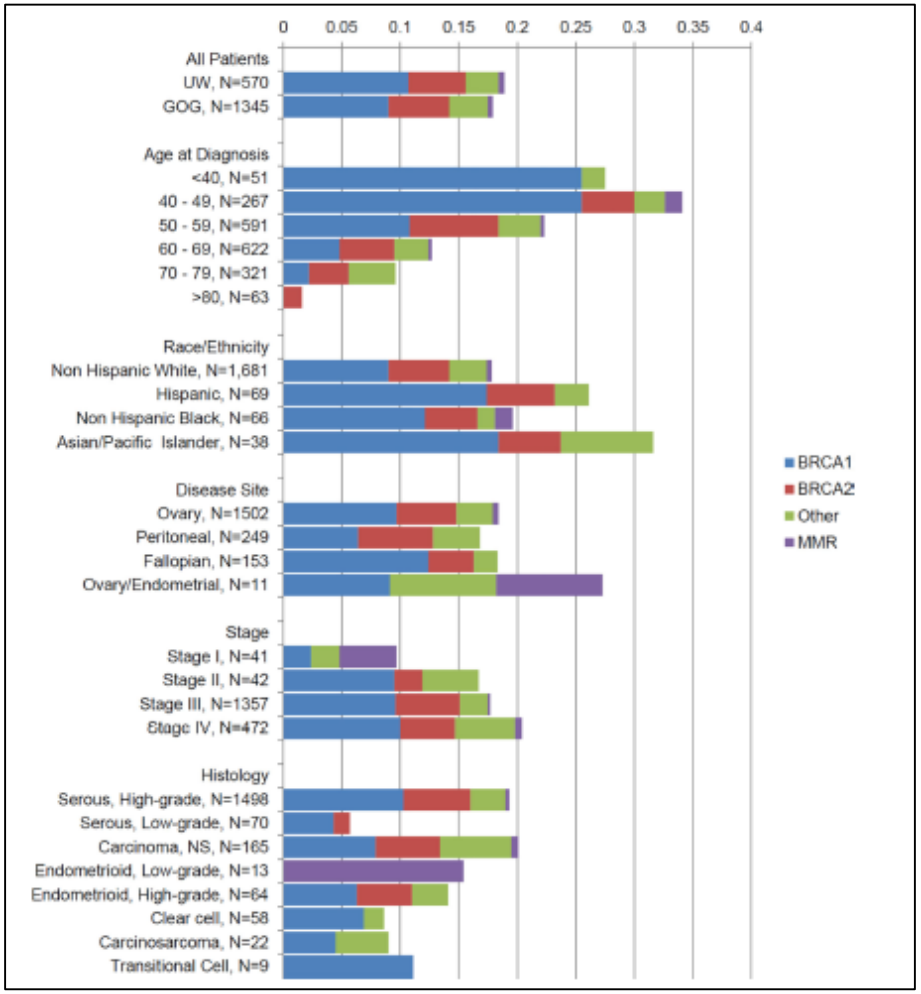
Breast Cancer	
Dx < 50 years	20%
Dx > 50 years	7%
Ovarian Cancer	10%
Both Breast and Ovarian Cancer	90%

Causes of Hereditary Susceptibility to Ovarian Cancer



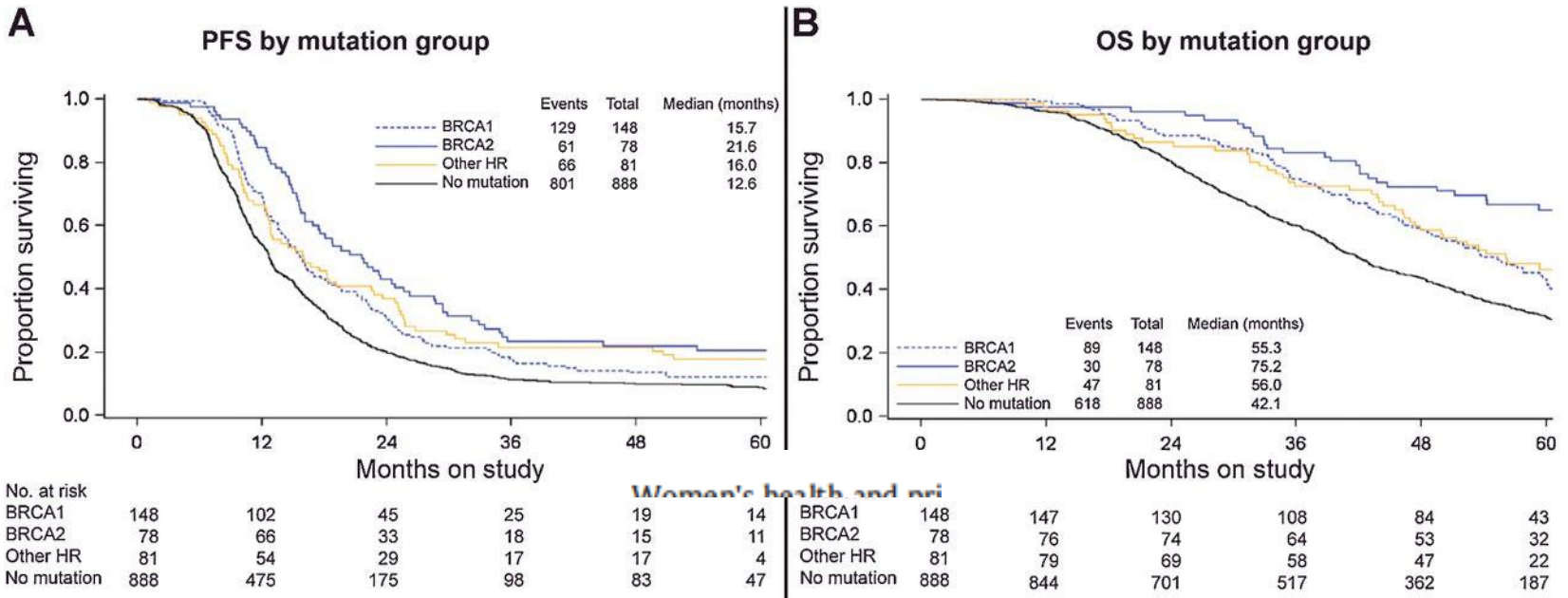
Inherited Mutations in Women with Ovarian Carcinoma

- 1915 subjects with OC: GOG218, GOG262, UW
- Germline DNA sequenced: targeted capture & multiplex sequencing assay BROCA
- 18% OC patients carried pathogenic genetic mutations:
  - 15% *BRCA1, BRCA2, MMR*
  - 3.3% *BRIP1, RD51C, RAD51D, PALB2, BARD1*
- OC patients with BRCA2 mutations had significantly better PFS (HR: 0.6) and OS (HR: 0.39)



Norquist B et al. JAMA Oncol. 2016 April 1; 2(4): 482–490

Progression-free and overall survival in ovarian carcinoma patients by mutation category.



Adjusted hazards for progression by mutation category

Gene category	Total *N*	Events (%)	aHR (95% CI)	*P* value
BRCA1	148	129 (87.2)	0.80 (0.66–0.97)	0.02
BRCA2	78	61 (78.2)	0.52 (0.40–0.67)	<0.0001
Other HRR	81	66 (81.5)	0.73 (0.57–0.94)	0.01
No mutation	888	801 (90.2)	1.0 (referent)	Referent

Adjusted hazards for death by mutation category

Gene category	Total *N*	Events (%)	aHR (95% CI)	*P* value
BRCA1	148	89 (60.1)	0.74 (0.59–0.94)	0.01
BRCA2	78	30 (38.5)	0.36 (0.25–0.53)	<0.0001
Other HRR	81	47 (58.0)	0.67 (0.49–0.90)	0.007
No mutation	888	618 (69.6)	1.0 (referent)	Referent

Barbara M. Norquist et al. Clin Cancer Res 2018;24:777-783

Clinical Cancer Research
AACR American Association for Cancer Research

Single-Gene vs Multigene (Panel) Testing

Single-Gene Testing

- Tests for mutation-specific gene
- PCR and direct sequencing
- Traditionally used when personal or FH suggests single inherited cancer syndrome

Panel Testing

- Tests mutation status of multiple genes with one sample
- Most commonly using NGS
- Can be used in place of single-gene testing; should be considered when negative for single-gene test but FH suggests an inherited susceptibility

Slide credit: clinicaloptions.com

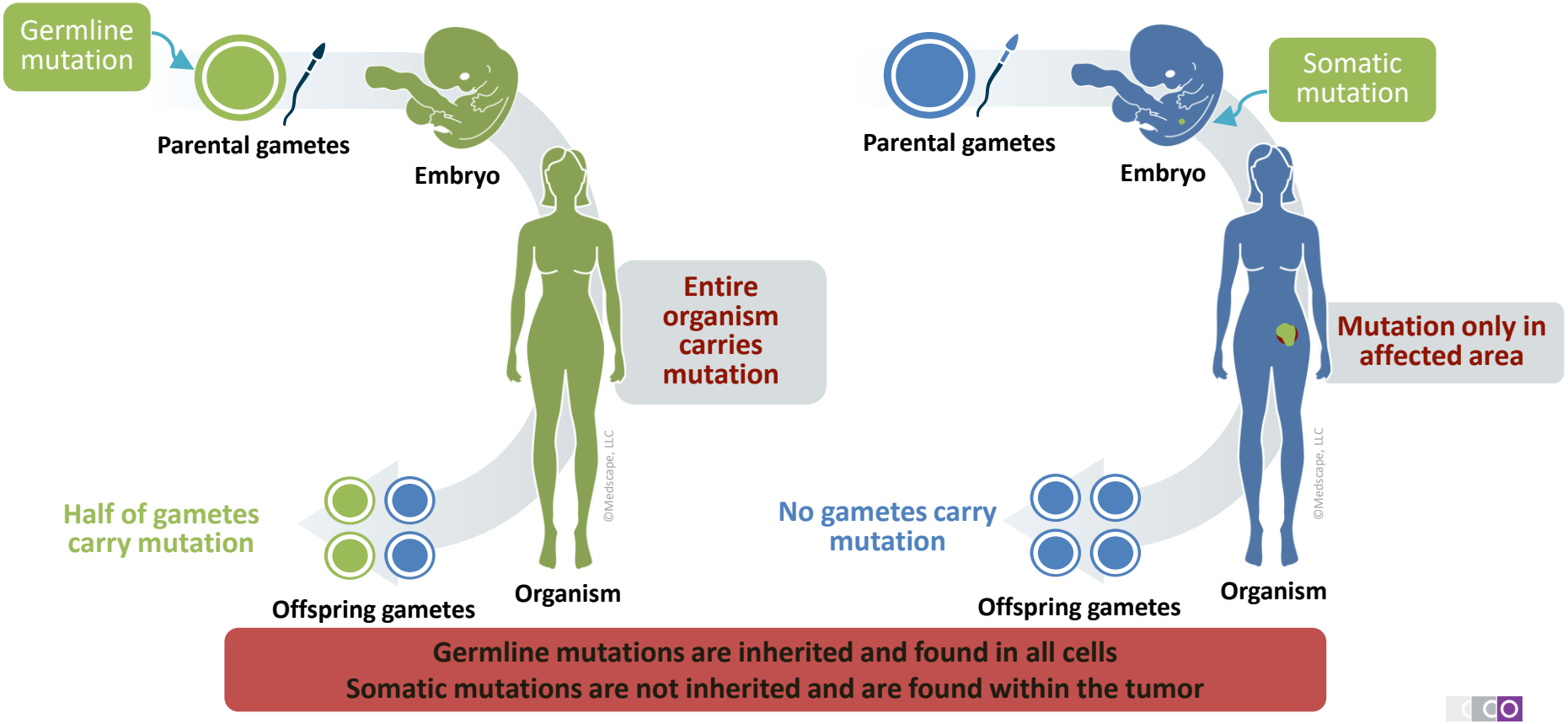
What test to use?

- Type of testing
  - Specific mutation testing if familial deleterious mutation is known
  - Comprehensive sequencing if familial mutation not known
  - Consider multigene testing (moderate risk genes) if mutation not known

Panel testing

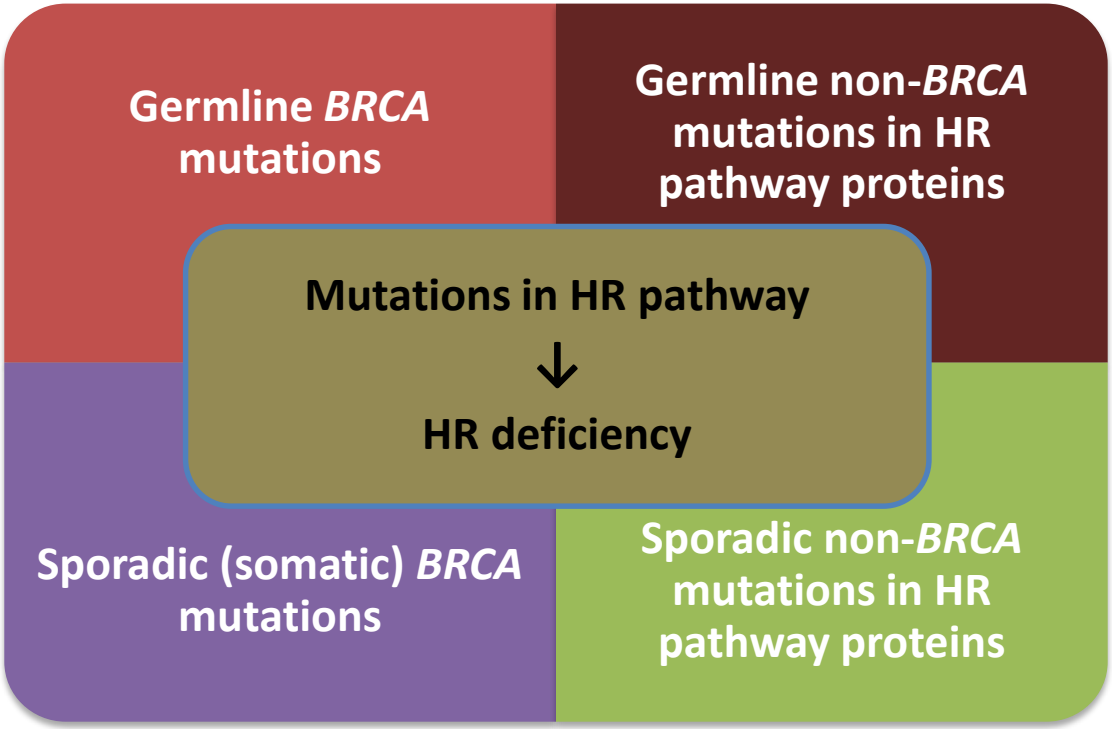
- NCCN guidelines for risk reducing surgery:
  - *BRCA1, BRCA2*, Lynch gene mutations
  - *RAD51c, RAD51D, BRIP1*
- Risk not increased for mutations in:
  - *ATM, CDH1, CHECK2, NF1*
- Risk uncertain*:*
  - *NBN, PALB2*

Germline vs Somatic Mutations



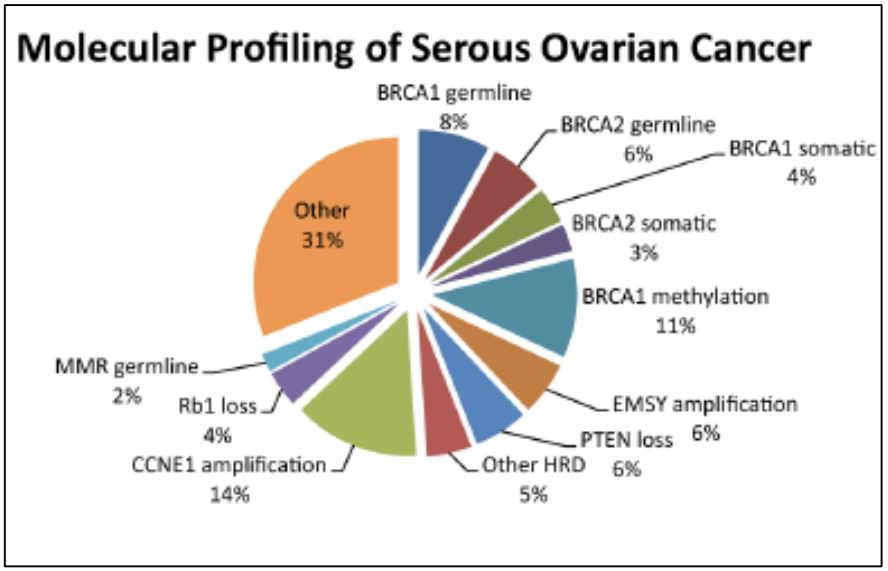
Slide credit: clinicaloptions.com

BRCA Mutations: Basic Concepts



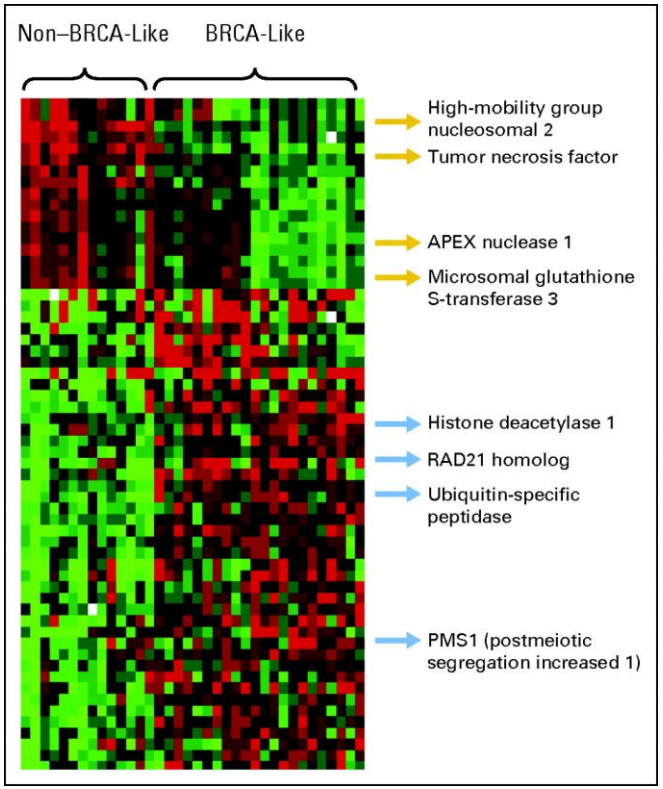
Slide credit: clinicaloptions.com

Mutations in Ovarian Ca

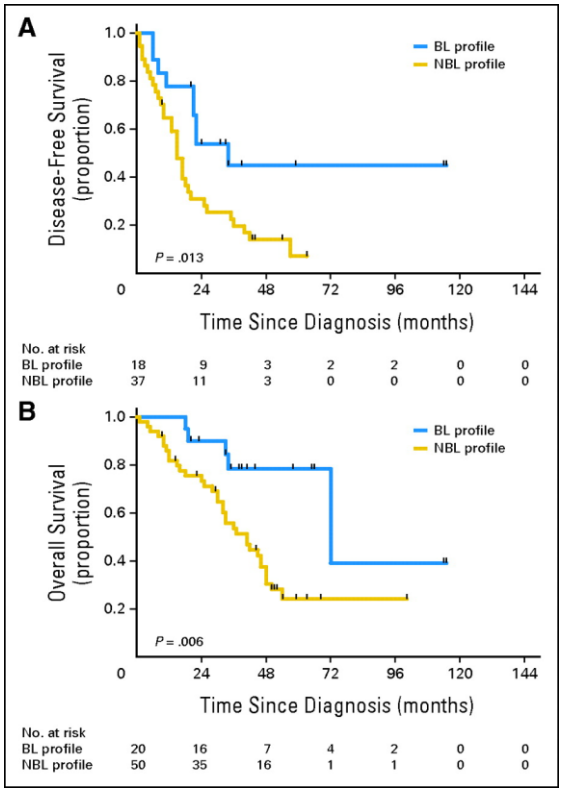


- Endometrioid: ARID1A, CTNNB1, PTEN, PIK3CA
- Clear cell: ARID1A, PIK3CA
- Low grade serous: KRAS, BRAF, ERBB2
- Mucinous: KRAS

BRCA testing
Ovarian Cancer



Expression plot of the 60 genes that comprise the BRCAness profile



Association of BRCAness profile with (DFS) and overall survival (OS)

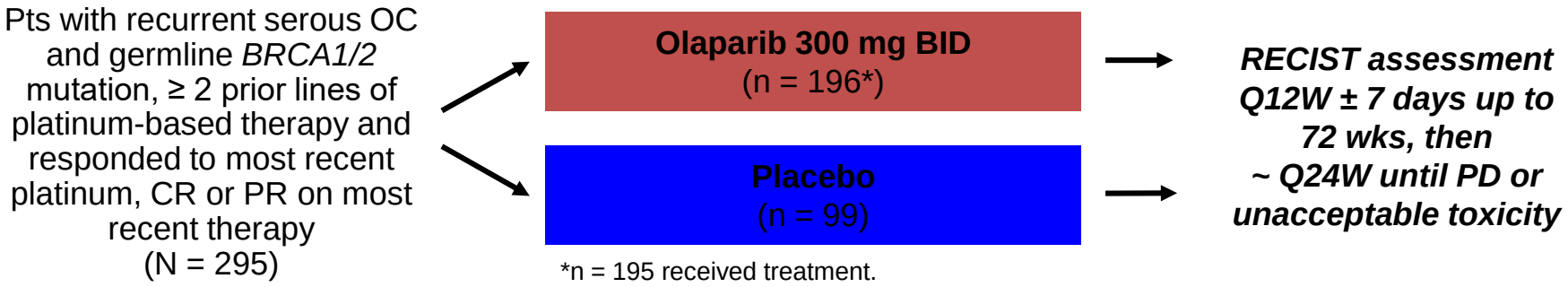
Konstantinopoulos, P. A. et al. J Clin Oncol; 28:3555-3561 2010

WHY DO GENETIC TESTING IN OVARIAN CANCER?

IT INFLUENCES TREATMENT DECISION

SOLO-2: Study Design

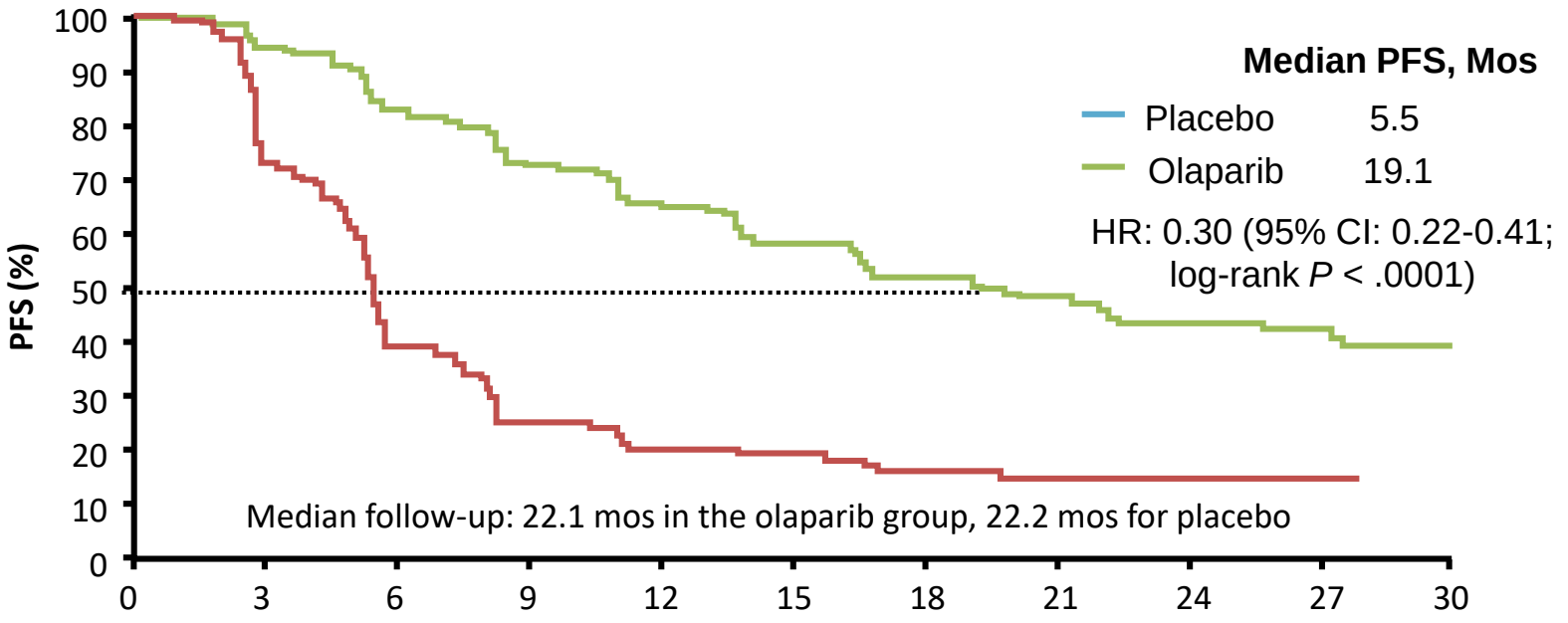
- International, randomized, double-blind phase III trial[1]



- Primary endpoint: investigator-assessed PFS
- Key secondary endpoints: safety/tolerability, PFS2, TFST, TSST, OS, HRQoL
- HRQoL analyses:
  - Primary: change in FACT-O TOI
  - Secondary pt-centered benefits: QAPFS (PFS + EQ-5D-5L); TWiST (mean PFS - mean toxicity)

1. Pujade-Lauraine E, et al. SGO 2017. Abstract LBA2. 2. Ledermann JA, et al. ASCO 2017. Abstract 5518. 3. Friedlander M, et al. ASCO 2017. Abstract 5507.

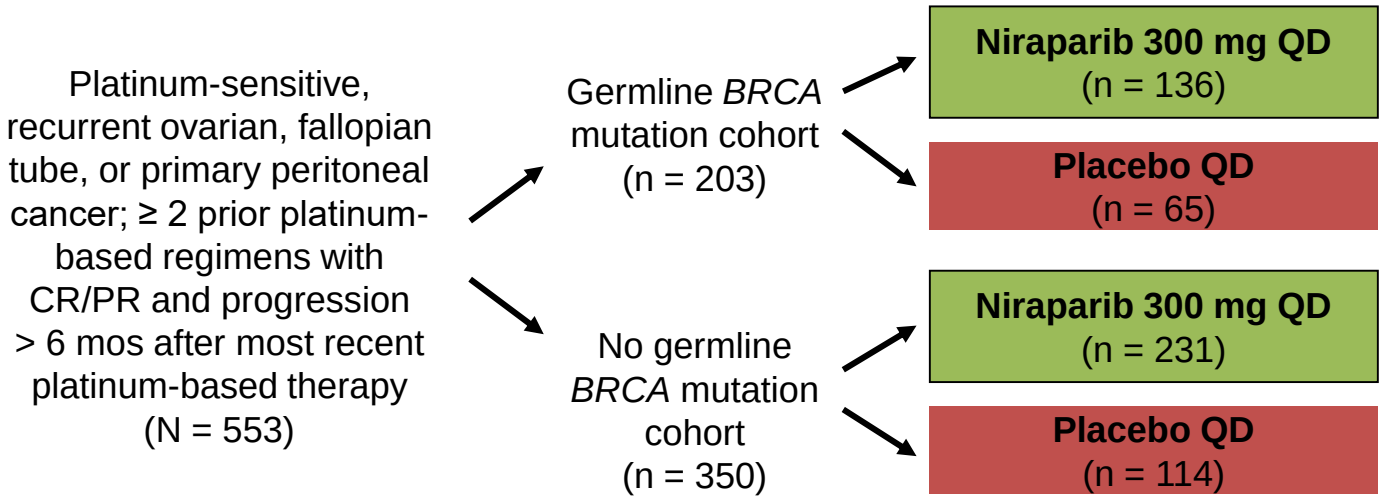
SOLO-2: PFS by Investigator Assessment



Pts at Risk, n											
Olaparib	196	182	156	134	118	104	89	82	32	29	3
Placebo	99	70	37	22	18	17	14	12	7	6	0

Pujade-Lauraine E, et al. SGO 2017. Abstract LBA2.

Phase III NOVA: Niraparib Maintenance in Platinum-Sensitive Ovarian Cancer



- Primary endpoint: PFS
- Secondary endpoints: chemotherapy-free interval, time to first subsequent therapy, PFS2, time to second subsequent therapy, OS
- Maintenance therapy initiated within 8 wks of last dose of platinum chemotherapy

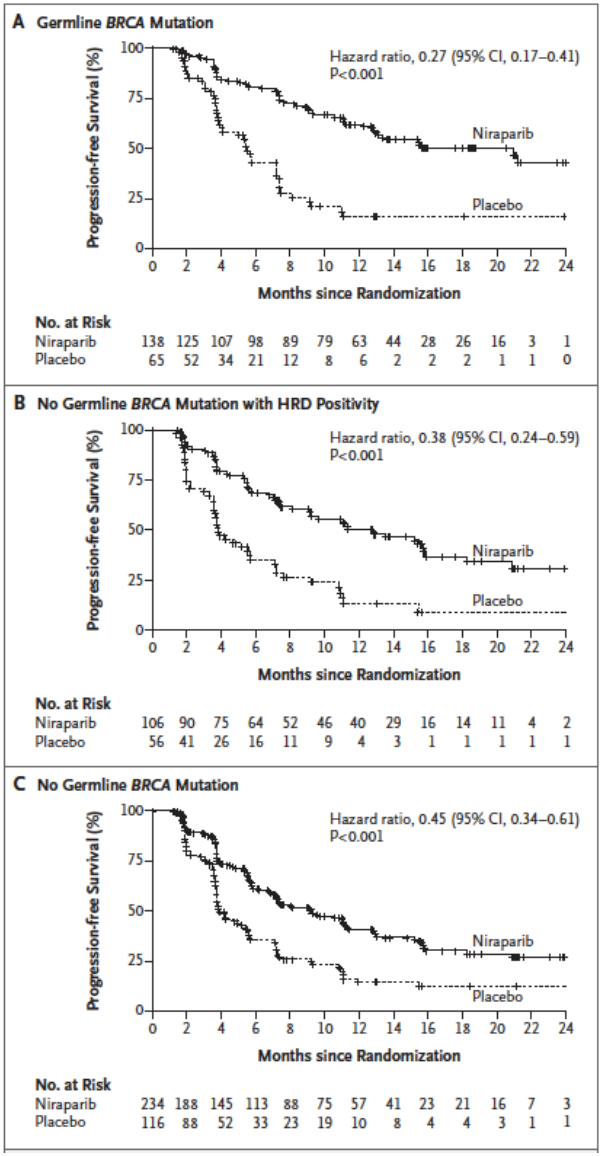
Mirza MR et al. NEJM 2016 375;22

Slide credit: clinicaloptions.com

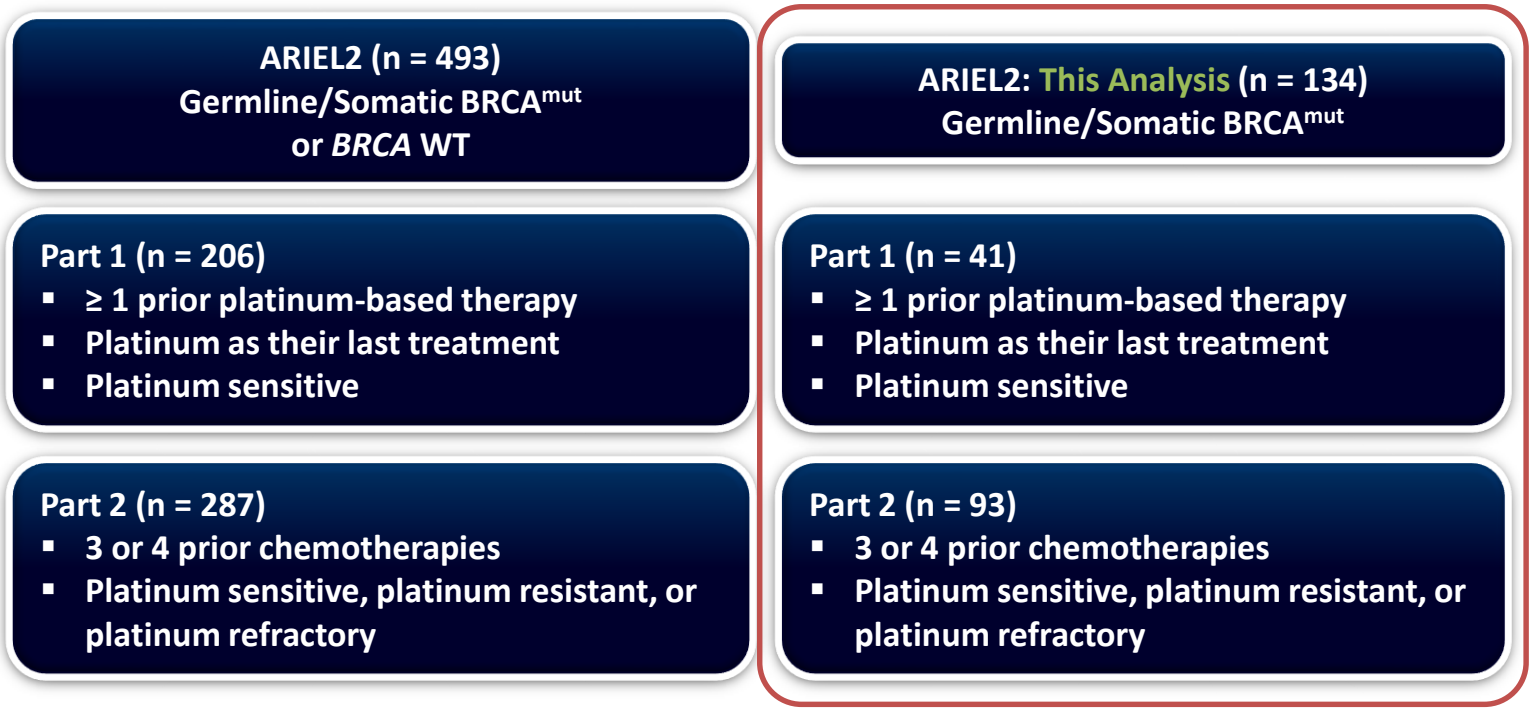
NOVA- Progression-Free Survival

- PFS significantly longer in all patients who received niraparib:
  - *gBRCA* 21.0 vs. 5.5 months (HR: 0.27; 95% confidence interval [CI], 0.17 to 0.41)
  - HRD 12.9 vs. 3.8 months (HR: 0.38; 95% CI, 0.24 to 0.59)
  - non *gBRCA* 9.3 vs. 3.9 months (HR: 0.45; 95% CI, 0.34 to 0.61)

    (P<0.001 for all 3 comparisons)



ARIEL2 Analysis: Pts With Mutated Germline or Somatic *BRCA*

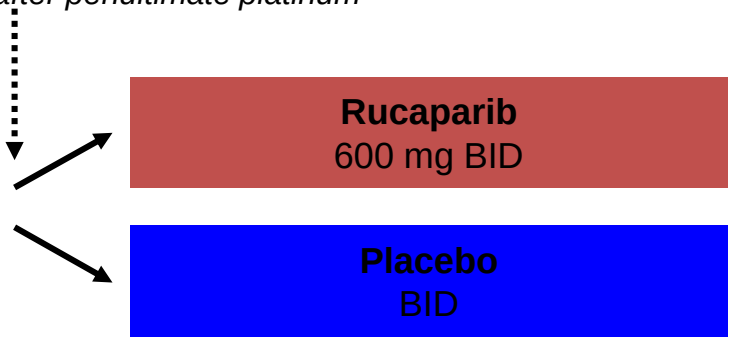


Konecny GE, et al. SGO 2017. Abstract 1.

Phase III ARIEL3: Rucaparib Maintenance in Platinum-Sensitive Ovarian Cancer

Stratified by HRD classification, response to platinum regimen, PFI after penultimate platinum

Pts with high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer after ≥ 2 prior platinum regimens, sensitive to penultimate platinum regimen, response to most recent platinum regimen, CA-125 ≤ ULN, ECOG PS 0-1, no prior PARP inhibitor
(Planned N = 540)



Primary endpoint: PFS in molecularly defined subgroups

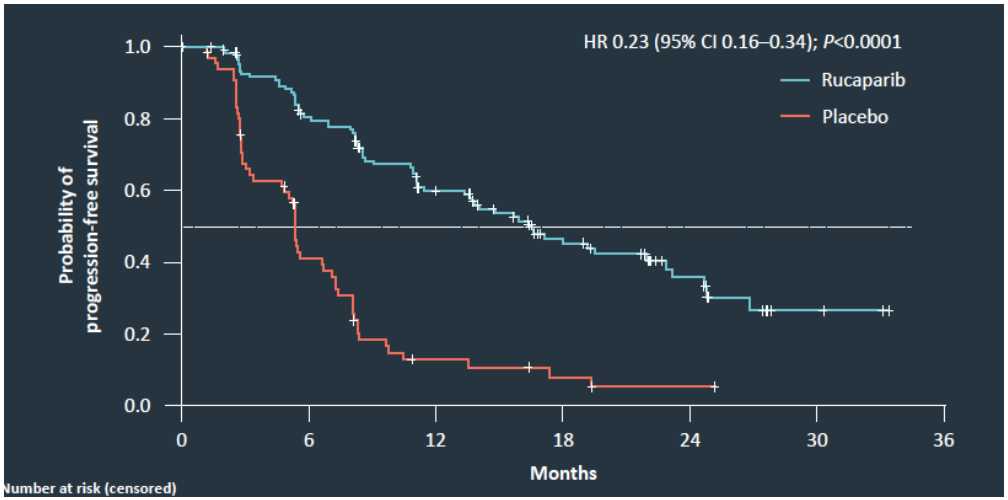
Secondary endpoints:

- OS
- PFS by independent radiology
- Pt-reported outcomes
- Safety

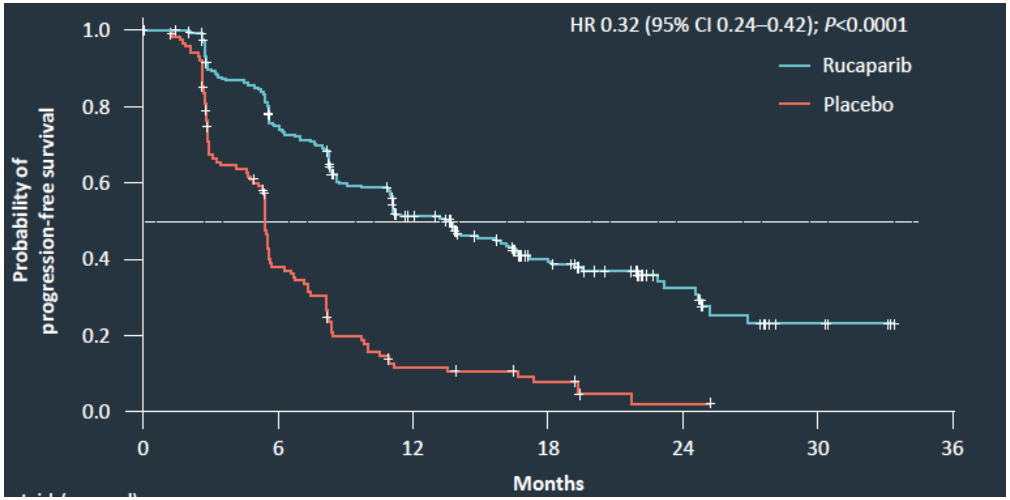
Clinicaltrials.gov. NCT01968213.

Slide credit: clinicaloptions.com

ARIEL 3- Progression-Free Survival



BRCA mutatnt Population



HRD Population

PARP Inhibitor Summary: Current Indications

	Olaparib[1]	Niraparib[2]	Rucaparib[3]
Approval date	December 2014, August 2017	March 2017	December 2016
Current indication	**Maintenance tx for recurrent disease in CR or PR to platinum tx** **g*BRCA*+ pts with ≥ 3 lines of tx**	**Maintenance tx for recurrent disease in CR or PR to platinum tx**	**Somatic or g*BRCA*+ pts with ≥ 2 lines of tx**
Dose and schedule	300 mg (two 150-mg tablets) PO BID	300 mg (three 100-mg capsules) PO QD	600 mg (two 300-mg tablets) PO BID
Safety	**MDS/AML** confirmed in 2% **Pneumonitis**, including fatal cases, occurred in < 1%	**Thrombocytopenia** (61%; 29% grade ≥ 3) **Neutropenia** (30%; 20% grade ≥ 3) **Hypertension** (20%; 9% grade ≥ 3)	**Elevated AST/ALT** (75%; 5%-13% grade ≥ 3) **Dysgeusia** (39%)
	Most common tx-related AEs include fatigue (60% to 80%); GI symptoms: nausea (65% to 75%), vomiting (35% to 45%), diarrhea (20% to 35%), pain (30% to 40%); and anemia (35% to 50%)		

1. Olaparib [package insert]. 2017. 2. Niraparib [package insert]. 2017.
3. Rucaparib [package insert]. 2017.

Slide credit clinicaloptions.com

Genetic Testing: Timing Recommendations

- NCCN guidelines: Germline panel testing at diagnosis in all women with ovarian, peritoneal and fallopian tube cancer

- Precision Medicine- Somatic testing on tumors at recurrence
  - *BRCA*, HRD, MSI, etc

Barriers to Testing

Barrier(s)	Proposed solutions
Provider-mediated	
Lack of awareness of testing benefit Lack of time during patient encounter Concerns over cost Perception that information detrimental to patient well-being	Provider education, reinforcement of societal recommendations
Payor-associated	
Lack of reimbursement for genetic counseling services Lack of reimbursement for genetic tests	Payment reform
System-associated	
Lengthy authorization processes Lack of infrastructure/staff to process authorizations Lack of tracking mechanisms to monitor execution of physician orders for testing	Research into optimal operational processes
Patient-associated	
Misunderstanding of counseling/testing intent Disinterest in results Fear of social or financial discrimination Racial disparities in testing due to education and access	Public education through public and professional societal advocacy Payment reform

L.M. Randall et al. / Gynecologic Oncology 146 (2017) 217–224

Thank you

Genetics
BRCA testing

- Testing criteria NCCN guidelines- 2016
  - Individual from a family with a known deleterious BRCA1/BRCA2 gene mutation
  - Personal hx of breast cancer + one or more of the following
    - Dx ≤45 y
    - D ≤50 y with: an additional criterion
    - Dx <60 triple negative
    - Dx at any age with other family members with ca breast, ovary, pancreas
  - Personal hx of ovarian cancer
  - Personal history of male breast cancer