BRCA Diagnostics n Ovarian Cancer

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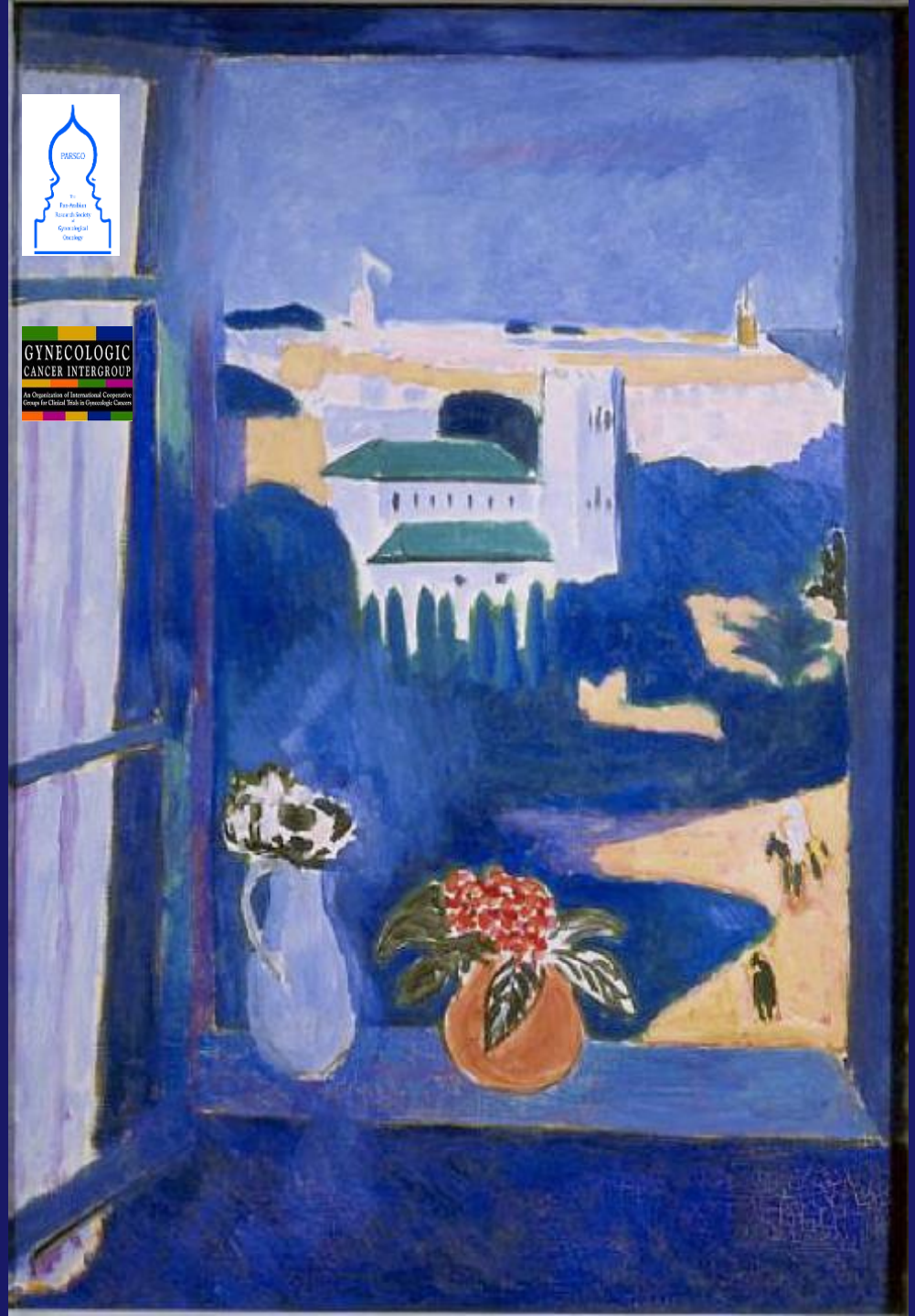

PARSGO
GYNECOLOGIC
CANCER INTERGROUP
An Organization of International Cooperative
Groups for Clinical Trials in Gynecologic Cancers

5. Ovarian Cancer Consensus Conference November 7 – 9th 2015 Tokyo, Japan

A1-3. What are the most important factors to be evaluated prior to initial therapy?

Biomarkers

1. Germline mutation testing to include BRCA1/2 is recommended for all patients enrolled on clinical trials

- Stratification (if possible) should be performed and knowledge of mutation status should be incorporated into primary endpoint analysis.
- Somatic mutation analysis for BRCA 1/2 is recommended

A3-1. Are there specific considerations for special patient subpopulations?

1. Race/Ethnicity
   Collection, reporting, and analysis of race/ethnicity categories
2. should be incorporated in future trials
3. There are emerging data that support differences in clinical outcomes in relationship to race/ethnicity, but pharmacogenomic markers have not been defined, and these population-based data are not sufficient to recommend stratification.

   As data are validated within specific populations, race/ethnicity

Eur Cancer 2016 Dec;69:127-134. doi: 10.1016/j.ejca.2016.10.006. Epub 2016 Nov 4.

Current perspectives on recommendations for BRCA genetic testing in ovarian cancer patients.

Vergote I, Banerjee S, Gerdes AM, van Asperen C, Marth C, Vaz F, Ray-Coquard I, Stoppa-Lyonnet D, Gonzalez A, Sehouli J, Colombo N

Traditionally, BRCA genetic testing has been undertaken to identify patients and family members at future risk of developing cancer and patients have been referred for testing based on family history. However, the now recognised risk of ovarian cancer (OC) patients, even those with no known family history, harbouring a mutation in BRCA1/2, together with the first poly adenosine diphosphate ribose polymerase inhibitor (PARPi; olaparib [Lynparza]) being licenced for the treatment of BRCA-mutated OC, has led to reconsideration of referral criteria for OC patients. Provided here is a review of the existing data and guidelines in the European Union, relating to recommendations, as well as considerations, for the referral of OC patients for BRCA genetic testing. Based on this review of newly updated guidance and up-to-date evidence, the following is recommended: all patients with invasive epithelial OC (excluding borderline or mucinous), including those with fallopian tube and peritoneal cancers, should be considered as candidates for referral for BRCA genetic testing, irrespective of age; genetic testing should ideally be offered at diagnosis, although patients can be referred at any stage; retrospective testing should be offered to patients in long-term follow-up because of the implications for family members and individual future breast cancer risk;

and germline BRCA testing of a blood/saliva sample should initially be conducted and, if negative, tumour tissue should be tested (to identify non-germline [somatic] BRCA PARPi therapy candidates).

Prevalence of germline mutations in risk genes including *BRCA1/2* in consecutive ovarian cancer patients (AGO TR-1)

Philipp Harter, Jan Hauke, Florian Heitz, Alexander Reuss, Stefan Kommoss, Frederik Marmé, André Heimbach, Katharina Prieske, Lisa Richters, Alexander Burges, Guido Neidhardt, Nikolaus de Gregorio, Ahmed El-Balat, Felix Hilpert, Werner Meier, Rainer Kimmig, Karin Kast, Jalid Sehouli, Klaus Baumann, Christian Jackisch, Tjoung-Won Park-Simon, Lars Hanker, Sandra Kröber, Jacobus Pfisterer, Heidrun Gevensleben, Andreas Schnelzer, Dimo Dietrich, Tanja Neunhöffer, Mathias Krockenberger, Sara Y. Brucker, Peter Nürnberg, Holger Thiele, Janine Altmüller, Josefin Lamla, Gabriele Elser, Andreas du Bois, Eric Hahnen, Rita Schmutzler

PLoS One. 2017; 12(10):

METHODS

Prospective testing of consecutive patients with first diagnosis or platinum sensitive relapse of invasive epithelial OC in 20 AGO Study Group centers in Germany. Patients could be included up to 6 months after end of platinum-based chemotherapy.

Testing included 25 risk genes related to ovarian cancer:

Core genes: *ATM, BRCA1, BRCA2, CDH1, CHEK2, NBN, PALB2, RAD51C, RAD51D, TP53*

LYNCH associated: *MLH1, MSH2, MSH6, PMS2*

Risk genes: *BARD1, BRIP1, BUB1B, CHEK1, FAM175A, FANCM, MRE11A, PTEN, RAD50, STK11, XRCC2*

For next generation sequencing (NGS) analysis a customer-tailored Agilent SureSelect gene panel was used for target enrichment, followed by paired-end multiplexed sequencing on Illumina devices. Additionally, all samples were screened for large genomic rearrangements (LGR) in *BRCA1/2* by Multiplex Ligation-dependent Probe Amplification (MLPA).

A deleterious variant was defined as class 4/5 mutation according to IARC and a positive family history was defined as at least one relative with breast cancer or ovarian cancer or breast cancer in personal history.

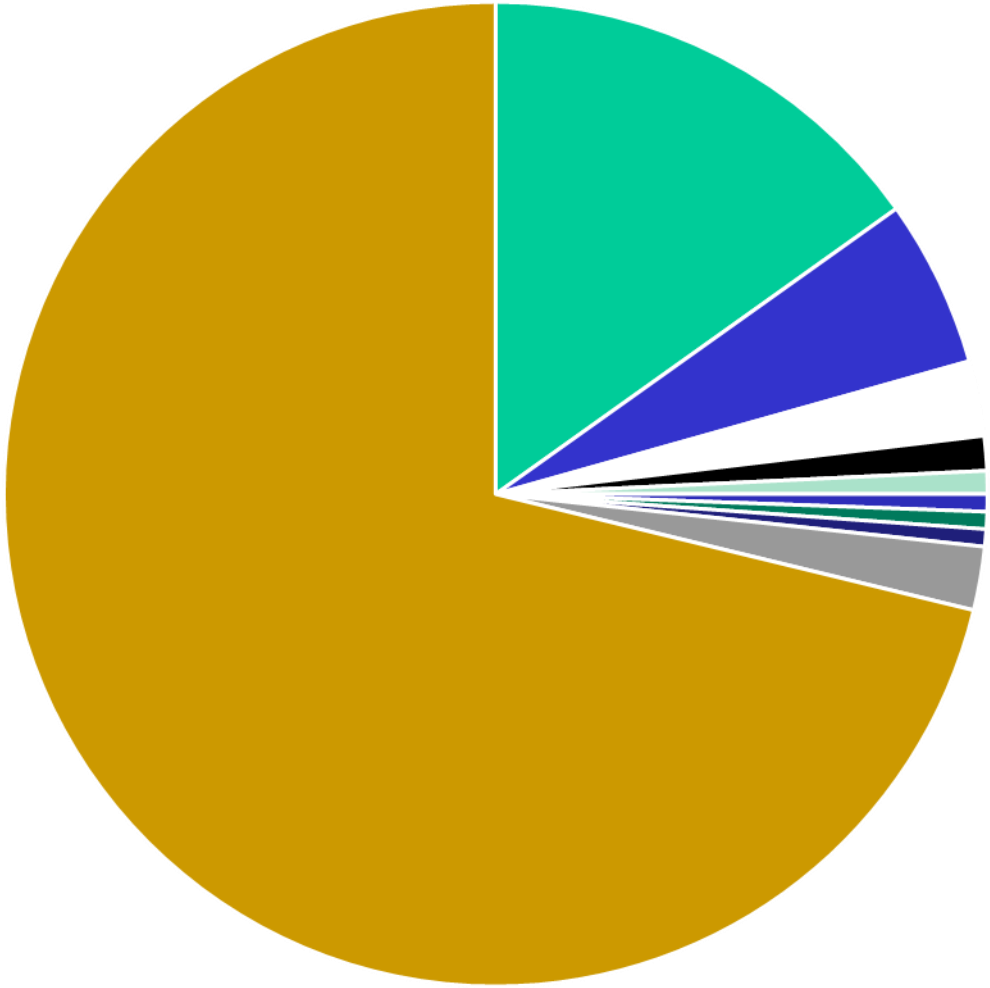
RESULTS I

FACTOR	ALL (n=522)	PRIMARY (n=281)	RELAPSE (n=241)
Age (mean, range) [years]	58 (16-93)	60 (18-93)	57 (16-82)
Family history positive (%)	225 (43.1)	119 (42.4)	106 (44.0)
Histologic subtype (%)			
- High grade serous	405 (77.6)	203 (72.2)	202 (83.8)
- High grade/G2-3 endometrioid	23 (4.4)	14 (5.0)	9 (3.7)
- Low grade serous	18 (3.5)	12 (4.3)	6 (2.5)
- Low grade/G1 endometrioid	7 (1.3)	5 (1.8)	2 (0.8)
- Clear cell	6 (1.2)	5 (1.8)	1 (0.41)
- Mucinous	9 (1.7)	4 (1.4)	5 (2.1)
- Others/unspecified	20 (3.8)	15 (5.3)	5 (2.1)
- Serous grade missing	25 (4.8)	15 (5.3)	10 (4.2)
FIGO stage at first diagnosis (%)			
- I-IIA	51 (9.8)	36 (12.8)	15 (6.2)
- IIB-IV	444 (85.1)	232 (82.6)	212 (88.0)
- missing	27 (5.2)	13 (4.6)	14 (5.8)

RESULTS II

FACTOR	ALL (n=522)	PRIMARY (n=281)	RELAPSE (n=241)
Any mutation (%)	146 (28.0)	70 (24.9)	76 (31.5)
Core genes (%)	140 (95.9)	65 (92.9)	75 (98.7)
- *BRCA1/2 (%)*	108 (20.7)	53 (18.9)	55 (22.8)
- - *BRCA1 (%)*	80 (15.3)	36 (12.8)	44 (18.26)
- - *BRCA2 (%)*	29 (5.6)	18 (6.4)	11 (4.6)
- *RAD51C (%)*	13 (2.5)	5	8
- *PALB2 (%)*	6 (1.1)	1	5
- *FANCM*	4	3	1
- *CHEK2*	3	1	2
- *RAD51D*	3	1	2
- LYNCH	3	3	0
-- *MSH2*	2	2	0
-- *MSH6*	1	1	0
- *ATM*	2	0	2
- *BRIP*	2	2	0
- *MRE11A*	2	2	0
- *NBN*	2	1	1
- *BUB1B*	1	0	1
- *CHEK1*	1	1	0
- *FAM175A*	1	0	1
- *RAD50*	1	1	0
- *XRCC2*	1	0	1
- *BARD1, CDH1, MLH1, PMS2, PTEN, STK11, TP53*	0	0	0

RESULTS III



BRCA1 BRCA2 RAD51C PALB2 FANCM
LYNCH CHEK2 RAD51D Others Negative

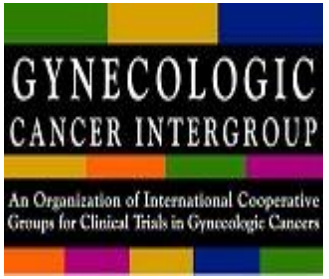
8 pts with 2 mutations		
1	*ATM*	*PALB2*
2	*BRIP1*	*CHEK2*
3	*BRCA2*	*FANCM*
4	*BRCA2*	*RAD50*
5	*BRCA2*	*BUB1B*
6	*BRCA1*	*XRCC2*
7	*BRCA1*	*NBN*
8	*BRCA1*	*BRCA2*

RESULTS IV

FACTOR	n	*BRCA1/2* positive	Any mutation	Wild type
All (%)	**522**	**108 (20.7)**	**146 (28.0)**	**376 (72.0)**
Age				
< 60 years	267	80 (30.0)	93 (34.8)	174 (65.2)
≥ 60 years	254	27 (10.6)	52 (20.5)	202 (79.5)
Family history				
Positive	225	71 (31.6)	82 (36.4)	143 (63.6)
Negative	288	33 (11.5)	59 (20.5)	229 (79.5)
Histo-type				
High grade serous	405	93 (23.0)	123 (30.4)	282 (69.6)
Others	108	11 (10.2)	18 (16.7)	90 (83.3)
High grade serous				
Primary	203	46 (22.7)	57 (28.1)	146 (71.9)

CONCLUSION

- 28.0% of patients with ovarian cancer show a germline mutation
- The rate of germline *BRCA1/2* mutations is 20.7%
- Testing only for *BRCA1/2* will miss 7.3% of additional mutations
- Neither family history, nor age, nor histologic subtype are valid predictors
- Genetic testing should be offered to all patients with ovarian cancer including other known risk genes



... HELL IS WHERE

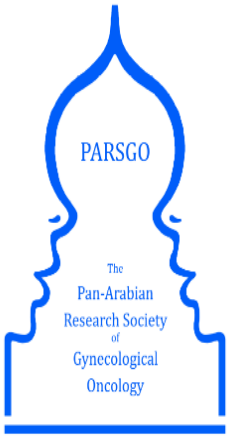
the cooks are British,

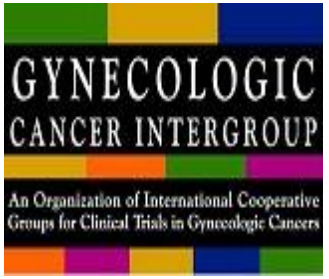
the police are German,

the mechanics are Spanish,

the lovers are Swiss,

and it´s all organized by the Italians.





... HEAVEN IS WHERE

the cooks are Morrocan,

the police are British,

the mechanics are German,

the lovers are Italian,

and it´s all organized by the Swiss.