



INSTITUTE
OF ONCOLOGY
LJUBLJANA



Združenje za
serologijo Slovenije
Slovenian Serological
Society



**WHAT'S NEW IN THE MANAGEMENT
OF *BRCA* POSITIVE OVARIAN AND
BREAST CANCER PATIENTS –**

2ND CONFERENCE

Grand Hotel Union Ljubljana, Slovenia
- Thursday, 19th of October 2017 -

SPEAKERS:

Judith Balmaña, Vall D'Hebron Institute of Oncology, Barcelona, Spain

Kathleen Claes, Ghent University, Belgium

Srdjan Novaković, Division of Molecular Diagnostics, Institute of Oncology Ljubljana, Slovenia

Mateja Krajc, Division of Cancer Genetic Counselling, Institute of Oncology Ljubljana, Slovenia

Ana Blatnik, Division of Cancer Genetic Counselling, Institute of Oncology Ljubljana, Slovenia

Ksenija Strojnik, Division of Cancer Genetic Counselling, Institute of Oncology Ljubljana, Slovenia

Erik Škof, Division of Medical Oncology, Institute of Oncology Ljubljana, Slovenia

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Roche

Ljubljana, 19th October 2017

PROGRAM:

15:30 – 16:00 *Participants gathering*

16:00 – 16:10 INTRODUCTION, **Mateja Krajc**

16:10 – 16:50 Cancer genetic counselling and testing in view of new treatment options/establishing new clinical pathways (Spanish experiences)
PARP inhibitors in breast cancer. a look back and a look forward (OlympiAD trial), **Judith Balmaña**

16:50 – 17:40 Cancer genetic counselling and testing in view of new treatment options/establishing new clinical pathways (Belgian experiences)
Tumor testing – where is its position in clinical pathways, **Kathleen Claes**

17:40 – 18:00 DISCUSSION

18:00 – 18:15 *Coffee Break*

18:15 – 19:15 HEREDITARY BREAST AND OVARIAN CANCER – SLOVENIAN EXPERIENCES

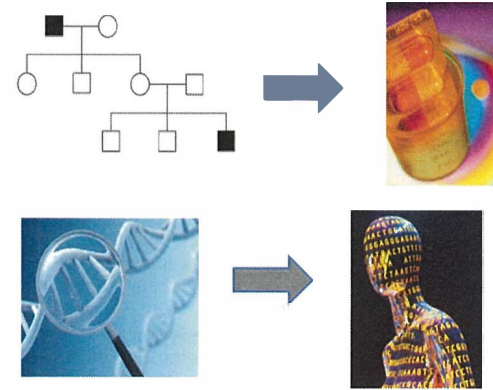
- HBOC – germline/ somatic genetic testing – laboratory experiences (latest updates), **Srdjan Novaković**
- Cancer genetic counselling – new clinical pathways in view of treatment options, **Ana Blatnik, Mateja Krajc and Ksenija Strojnik**
- Slovenian experiences with olaparib in ovarian cancer treatment, **Erik Škof and Maja Ravnik**
- PARP inhibitors in breast cancer – current and future perspectives in Slovenia, **Simona Borštnar**
- Surgical treatment of *BRCA* positive breast cancer patients – current practice and Slovenian results, **Janez Žgajnar**

19: 15 – 19:30 DISCUSSION

19:30 - *Dinner*

Cancer genetic counseling and testing in view of new treatment options/establishing new clinical pathways

Judith Balmaña
Clinical cancer genetics
Medical Oncology Department
Hospital Vall d'Hebron

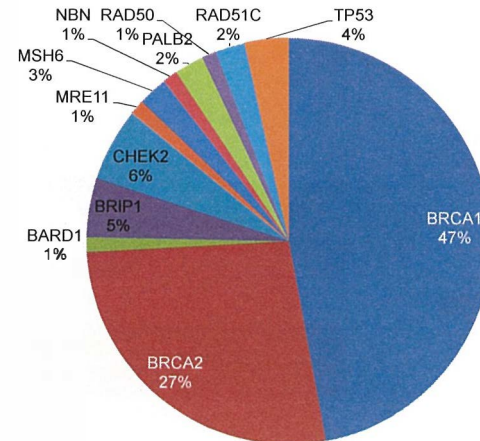


New paradigms

Teaching model: Directive
Disease-Based, Doctor-
Centered Medicine



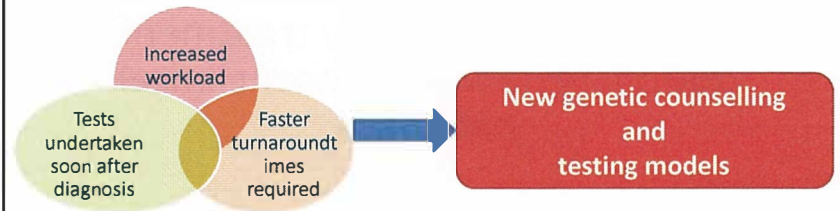
Counseling model: Non-
directive
Patient-centered Medicine



BRCA-targeted approved therapies

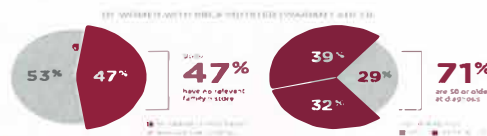
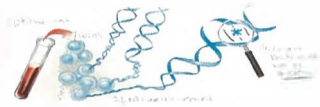
- Olaparib (Lynparza™, AstraZeneca)
 - EMA (Dec2014): Monotherapy maintenance treatment of platinum-sensitive relapsed **BRCA-mutated (germline and/or somatic)** high-grade serous ovarian cancer patients
 - FDA (Dec2014): Monotherapy for **germline BRCA1/2 mutated** advanced ovarian cancer patients who have been treated with minimum three prior lines of chemotherapy. Aug 2017: FDA approved olaparib as maintenance treatment of patients with recurrent epithelial ovarian cancer who are in a response to platinum-based chemotherapy.
- Rucaparib (Rubraca™, Clovis Oncology)
 - FDA (Dec2016) : Monotherapy for patients with advanced ovarian cancer and deleterious **BRCA mutation (germline and/or somatic)** who have been treated minimum two chemotherapies.
- Niraparib (Zejula™, Tesaro)
 - FDA (Mar2017) : Monotherapy for maintenance treatment of patients with recurrent epithelial ovarian cancer, whose tumours have a response to platinum-based chemotherapy.

Treatment implications

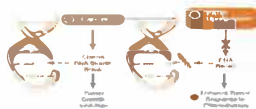


BRCA1/2 testing

BRCA mutations appear in:

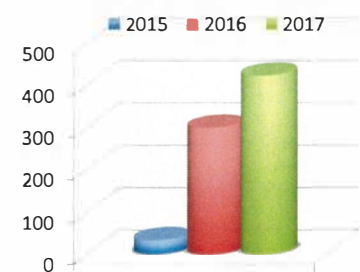
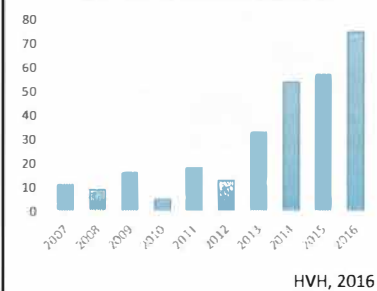


Change in testing criteria: BRCA testing for every patient with non-mucinous epithelial ovarian cancer



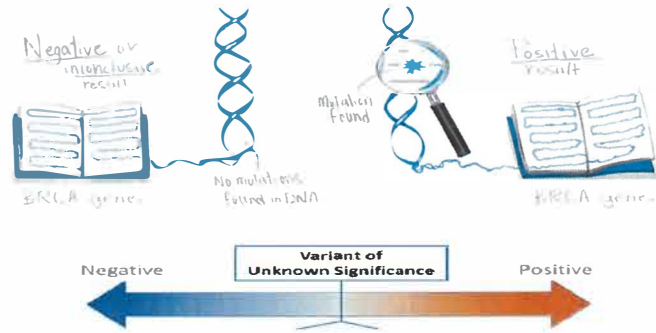
Zhang et al. Gynecologic Oncology (2011)

Ovarian Cancer Patients tested



M. De la Hoya
Personal communication, 2017

BRCA1/2 testing results



Treatment implication → New Genetic Counselling models

The 'DNA-direct' model (The Netherlands)

Telephone pretest GC → BRCA testing → Face-to-face posttest GC

Processing time is reduced. Similar psychological outcomes, but patients were not randomised

Telephone-based counselling model (USA)

Telephone pretest GC → BRCA testing → Telephone posttest GC

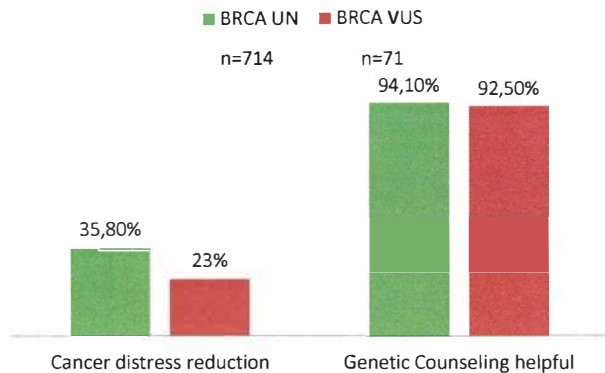
Lower uptake. Not recommended for newly diagnosed or metastatic cancer patients.

Royal Marsden testing model (UK)

Approved clinical explain BRCA testing → BRCA testing → Clinician gives results and refer to genetics if positive

Geneticists need to undertake online training

VUS and cancer distress



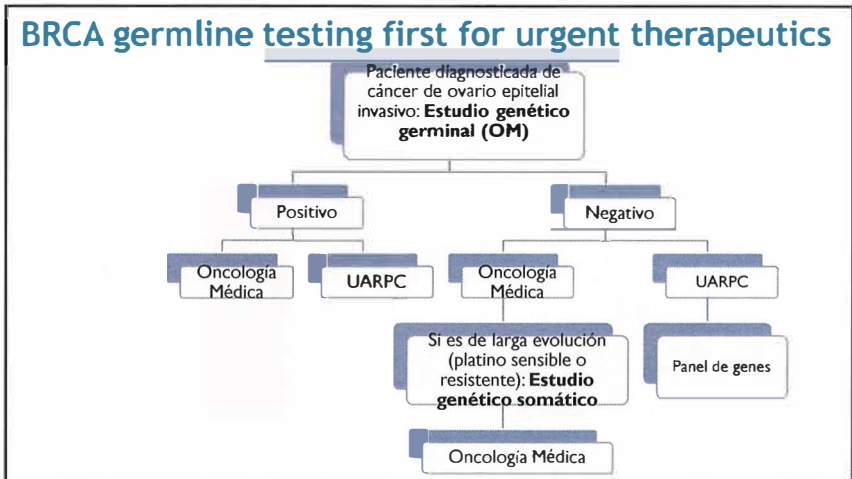
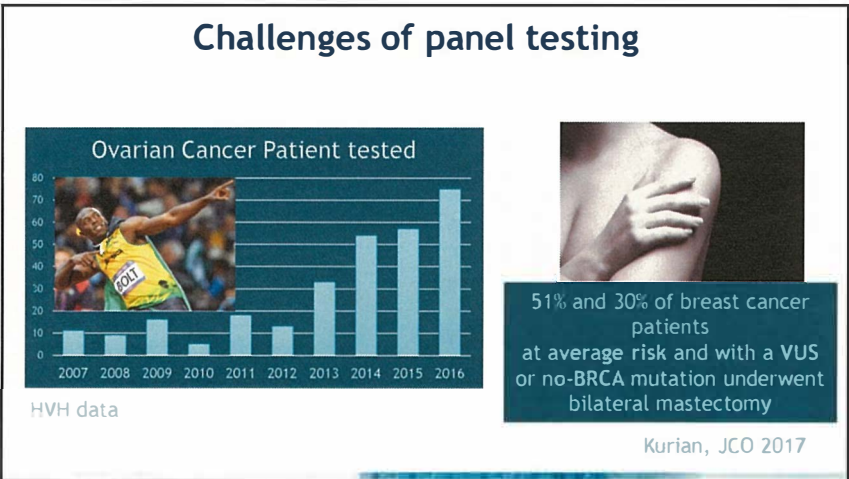
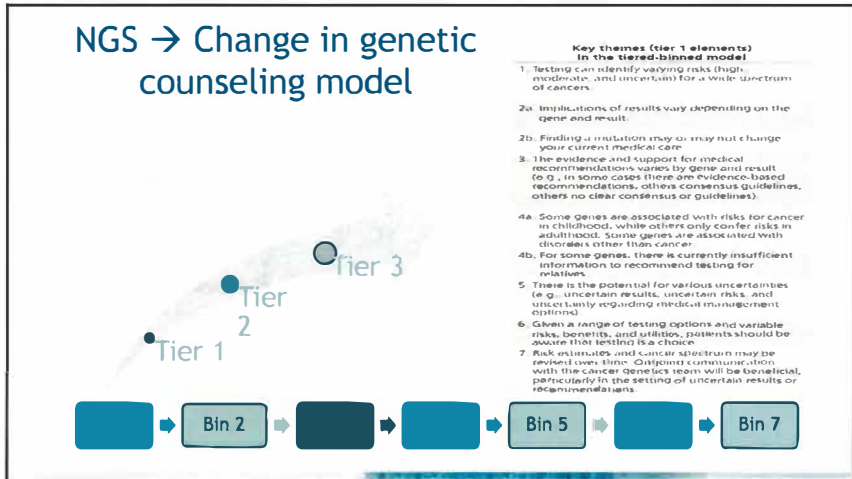
Curver et al. Clin Genet. 2013

Clinical validity for cancer risk assessment *BRIP1*, *RAD51C*, *RAD51D*

GENES	CASES	CONTROLS	MEAN AGE	RELATIVE RISK (95% CI)
<i>BRIP1</i>	0.9% 0.6%	0.09%	63.8y (93% >50y)	Seg. 3.4 (2-5) 5.8% at 80y cc. 11.2 (3-34)
<i>BARD1</i>	0.12%	0.06% (p=.39)	55.5 y (53-60)	-
<i>PALB2</i>	0.28%	0.09% (p=.08)	56 y (49-65)	-
<i>NBN</i>	0.28%	0.23% (p=.61)	NA	-
<i>RAD51C</i>	0.41%	0.07%	70% >50y	5.2 (1.1-24) 5% at 70y
<i>RAD51D</i>	0.35%	0.04%	92% >50y	12 (1.5-90) 12% at 70y

Gene	Mammography (clinical breast examination and/or breast MRI)	RRSO	Colonoscopy	Pancreatic screening
ATM	Annual starting at 40*	Family history ^d	Family history ^d	Clinical trial
CHEK2 (truncating)	Annual starting at 40**	Family history ^d	Discuss at 40 years	NA
NBN	Annual starting at 40*	Family history ^d	Family history ^d	NA
PALB2	Annual starting at 30	Family history ^d	Family history ^d	Clinical trial
BRIP1/RAD51C/RAD51D	Family history ^a	50-55 years ^a	Family history ^d	NA

Tung, Nature Reviews



Gene panel testing first

Paciente diagnosticada de cáncer de ovario
epitelial invasivo

UARPC: Panel
genes

Positivo

Negativo

OM: Si es de larga evolución (platino
sensible o resistente): **Estudio
genético somático**

PARP inhibitors in breast cancer - a look back and a look forward

Multidisciplinary units



Phase II/III studies with PARPi & biomarker analysis in breast cancer

1. Phase II: ABRAZO - talazoparib, mBC, gBRCA
Cohort 1: platinum-treated (ORR 21%)
Cohort 2: platinum-naïve,
but heavily pre-treated (ORR 37%)
2. Phase III: OlympiaAD – olaparib, mBC, gBRCA
3. Phase III: BRAVO – niraparib, mBC, gBRCA
4. Phase III: EMBRACA – talazoparib, mBC, gBRCA

Background

- Cancers arising in women with deleterious germline mutations in breast cancer susceptibility genes 1 or 2 (*BRCA1* and *BRCA2*) are deficient in DNA double-strand break repair and repair of stalled replication forks¹⁻³
 - These cells depend on poly (ADP-ribose) polymerase (PARP) for DNA repair
- PARP inhibitors
 - Inhibit PARP catalytic activity⁴
 - Trap PARP at sites of DNA damage⁴
 - Prevent DNA damage repair, resulting in cell death in *BRCA1/2*-mutated cancer cells

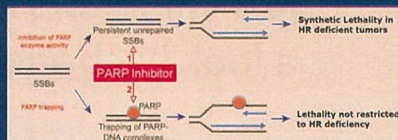


Figure adapted from Murali J et al. *Cancer Res*. 2012; 72:5088-5099, with permission from AACR

1. Ashworth A. *J Clin Oncol*. 2008;26:3785-3790. 2. Jalve M, Curtin NJ. *Ther Adv Med Oncol*. 2011;3:257-267. 3. Helleday T. *Mol Oncol*. 2011;5:387-393. 4. Lord CJ, Ashworth A. *Science*. 2017;355:1152-1158.

Phase 2 Clinical Trial – Key Eligibility Criteria

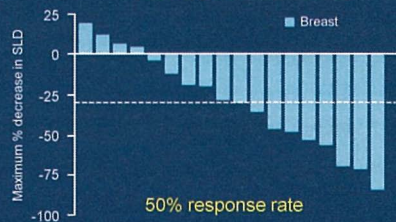
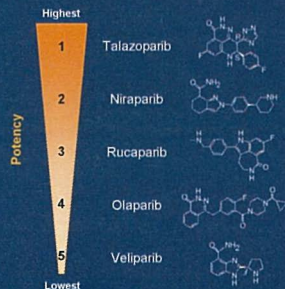
- Patients with advanced breast cancer who carry a deleterious or suspected deleterious germline *BRCA1/2* mutation (by central laboratory or a local report approved by the sponsor)
 - Cohort 1: PR or CR to last platinum-containing regimen for metastatic disease with disease progression > 8 weeks following the last dose of platinum
 - Cohort 2: 3 or more prior cytotoxic regimens for metastatic disease; no prior platinum for metastatic disease
- Measurable disease by RECIST v1.1
- ECOG performance status 0 or 1
- Adequate organ and bone marrow function
- CNS metastases permitted, provided stable following local therapy
- HER2+ breast cancer permitted, provided the patient's disease is refractory to HER2-targeted therapy
- Washout from prior therapy (systemic therapy, RT, surgery): 14 days

Abbreviations: CNS, central nervous system; CR, complete response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors version 1.1; RT, radiation therapy.

Background – Talazoparib

Talazoparib is a highly potent inhibitor of PARP¹

Phase 1 trial – 18 breast cancer patients with *BRCA1/2* germline mutations²



1. Lord CJ, Ashworth A. *Science*. 2017;355:1152-1158. 2. de Bono J et al. *Cancer Discov*. 2017 Feb 27. doi: 10.1158/2159-8290.CD-16-1250

Study Design

Objectives

- Primary endpoint: confirmed ORR by central independent radiology facility (IRF) using RECIST v1.1
- Secondary endpoints:
 - DOR, CBR lasting \geq 24 weeks, PFS, OS
 - Safety

Abbreviations: CBR, clinical benefit rate; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival

Select Baseline Characteristics

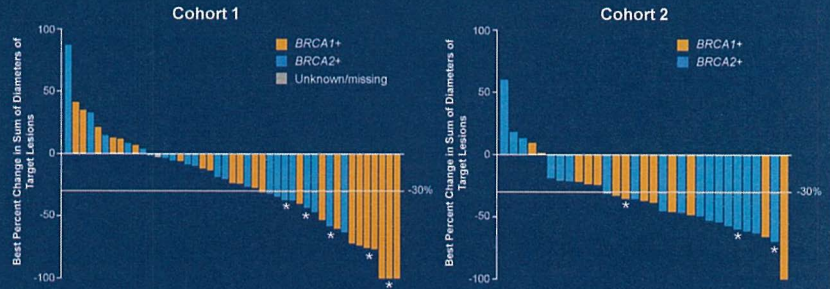
ITT Population

	Cohort 1 Prior Platinum (n = 49)	Cohort 2 3L+, No Prior Platinum (n = 35)	Total (N = 84)
Age, median (range), years	50 (31-74)	52 (33-75)	50 (31-75)
ECOG = 0, No. (%)	34 (69)	15 (43)	49 (58)
History of CNS metastasis, No. (%)	8 (16)	1 (3)	9 (11)
Visceral disease, No. (%)	38 (78)	23 (66)	61 (73)
Hormone receptor status, No. (%)			
HER2+	1 (2)	5 (14)	6 (7)
Triple-negative	29 (59)	6 (17)	35 (42)
ER+ or PR+	20 (41)	29 (83)	49 (58)
BRCA status, No. (%)			
BRCA1+	26 (53)	15 (43)	41 (49)
BRCA2+	22 (45)	20 (57)	42 (50)
Unknown	1 (2)	0	1 (1)

Abbreviations: ER+, estrogen receptor positive; ITT, intent-to-treat; PR+, progesterone receptor positive.

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Maximal Percent Change in Sum of Diameters of Target Lesions by BRCA Mutation Status



*Ongoing subjects as of data cutoff of September 1, 2016.

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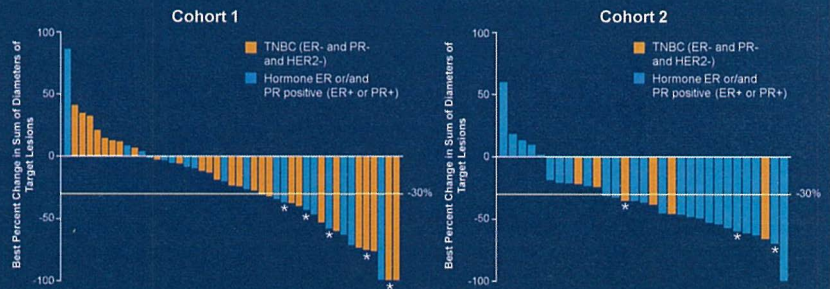
Primary Efficacy Endpoint – ORR by Independent Radiologist Facility

	Cohort 1 Prior Platinum (n = 48)	Cohort 2 3L+, No Prior Platinum (n = 35)	Total (N = 83)
Objective response rate, % (95% CI)	21 (10-35)	37 (22-55)	28 (18-39)
Best overall response, % (No.)			
Complete response	4 (2)	0	2 (2)
Partial response	17 (8)	37 (13)	25 (21)
Stable disease	38 (18)	51 (18)	43 (36)
Progressive disease	38 (18)	11 (4)	27 (22)
Not evaluable	4 (2)	0	2 (2)

Objective response using RECIST v1.1. Confirmation of CR and PR required.
Data cutoff for primary endpoint was September 1, 2016.
Abbreviation: CI, confidence interval.

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Maximal Percent Change in Sum of Diameters of Target Lesions by Hormone Receptor Status



*Ongoing subjects as of data cutoff of September 1, 2016.

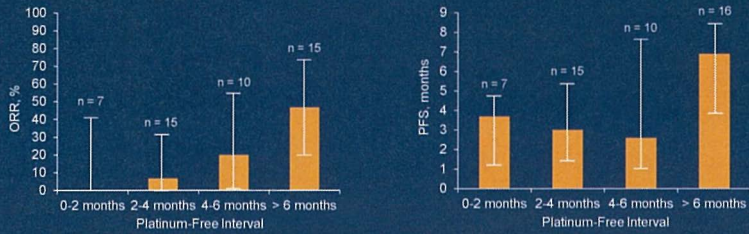
Abbreviation: TNBC, triple-negative breast cancer.

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Platinum-Free Interval

ITT Population in Cohort 1 (Patients Who Received Prior Platinum, n = 48)

- Median time from last platinum dose to progression was 4.0 months (range, 0.03-49.15)



Safety – Nonhematologic

All TEAEs in ≥ 20% of patients and G3+ TEAEs in ≥ 5% of patients

	Cohort 1 Prior Platinum (n = 48)			Cohort 2 3L+, No Prior Platinum (n = 35)		
	All Grade	Grade 3	Grade 4	All Grade	Grade 3	Grade 4
Number of patients ≥ 1 TEAE, No. (%)	47 (97.9)	13 (27.1)	2 (4.2)	34 (97.1)	11 (31.4)	3 (8.6)
Fatigue	29 (60.4)	3 (6.3)	0	8 (22.9)	0	0
Nausea	20 (41.7)	2 (4.2)	0	15 (42.9)	0	0
Diarrhea	17 (35.4)	1 (2.1)	0	10 (28.6)	0	0
Decreased appetite	11 (22.9)	1 (2.1)	0	9 (25.7)	0	0
Dyspnea	11 (22.9)	1 (2.1)	1 (2.1)	9 (25.7)	2 (5.7)	0
Atopecia (grade 1)	11 (22.9)	0	0	7 (20.0)	0	0
Back pain	11 (22.9)	0	0	7 (20.0)	0	0
Vomiting	10 (20.8)	0	0	7 (20.0)	0	0
Pleural effusion	4 (8.3)	3 (6.3)	0	4 (11.4)	2 (5.7)	0

No grade 5 TEAEs were observed.

Safety – Hematologic

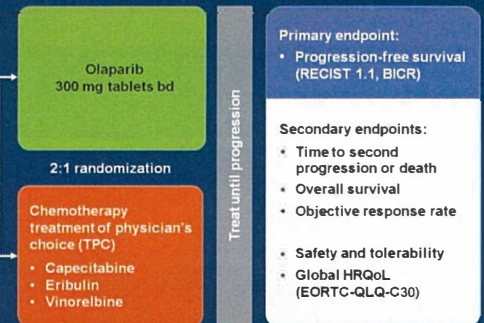
All TEAEs in ≥ 15% of patients and G3+ TEAEs in ≥ 5% of patients

	Cohort 1 Prior Platinum (n = 48)			Cohort 2 3L+, No Prior Platinum (n = 35)		
	All Grade	Grade 3	Grade 4	All Grade	Grade 3	Grade 4
Number of patients ≥ 1 TEAE, No. (%)	31 (64.6)	23 (47.9)	2 (4.2)	23 (65.7)	15 (42.9)	2 (5.7)
Anemia	24 (50.0)	16 (33.3)	0	19 (54.3)	13 (37.1)	0
Thrombocytopenia	18 (37.5)	8 (16.7)	2 (4.2)	9 (25.7)	4 (11.4)	2 (5.7)
Neutropenia	10 (20.8)	6 (12.5)	0	12 (34.3)	6 (17.1)	0
Leukopenia	7 (14.6)	1 (2.1)	0	6 (17.1)	2 (5.7)	0

No grade 5 TEAEs were observed.

OlympiAD study design

- HER2-negative metastatic BC
 - ER+ and/or PR+ or TNBC
- Deleterious or suspected deleterious gBRCAm
- Prior anthracycline and taxane
- ≤ 2 prior chemotherapy lines in metastatic setting
- HR+ disease progressed on ≥ 1 endocrine therapy, or not suitable
- If prior platinum use
 - No evidence of progression during treatment in the advanced setting
 - ≥ 12 months since (neo)adjuvant treatment

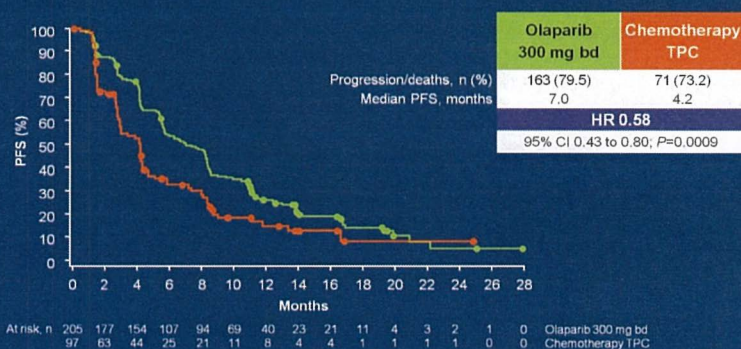


BICR, blinded independent central review; ER, estrogen receptor; HRQoL, health-related quality of life; PR, progesterone receptor; RECIST, response evaluation criteria in solid tumors; TNBC, triple negative breast cancer

Patient characteristics

	Olaparib 300 mg bd (N=205)	Chemotherapy TPC (N=97)
Age, years (median, range)	44 (22–76)	45 (24–68)
Male, n (%)	5 (2)	2 (2)
White race, n (%)	134 (65)	63 (65)
BRCA mutation status, n (%)		
BRCA1	117 (57)	51 (53)
BRCA2	84 (41)	46 (47)
Both	4 (2)	0
Hormonal receptor status, n (%)		
ER+ and/or PR+	103 (50)	49 (51)
TNBC	102 (50)	48 (49)
Prior chemotherapy for metastasis, n (%)	146 (71)	69 (71)
Prior platinum treatment, n (%)	60 (29)	26 (27)

Primary endpoint: progression-free survival by BICR

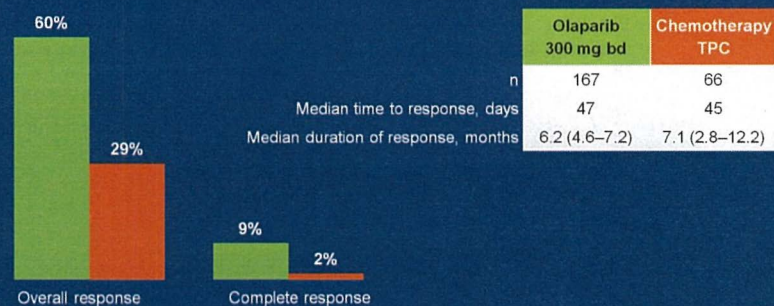


Patient characteristics

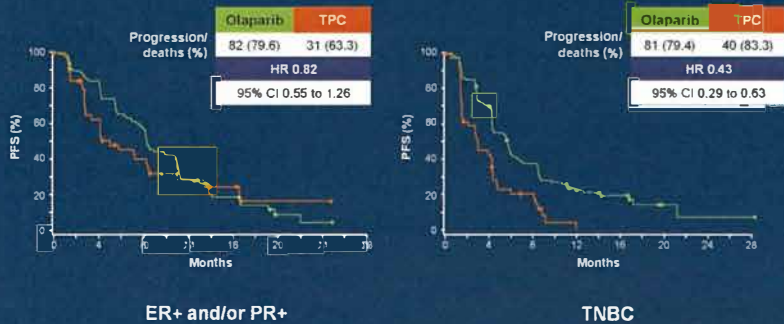
n (%)	Olaparib 300 mg bd (N=205)	Chemotherapy TPC (N=97)
<i>De novo</i> metastatic breast cancer	26 (13)	12 (12)
Measurable disease	167 (82)	66 (68)
≥2 sites	159 (78)	72 (74)
Bone metastases only	16 (8)	6 (6)
Prior lines of chemotherapy for metastases		
0	68 (33)	31 (32)
1	80 (39)	42 (43)
2	57 (28)	24 (25)
Chemotherapy TPC*		
Capecitabine	NA	41 (45)
Eribulin		34 (37)
Vinorelbine		16 (18)

*6 patients did not receive study treatment

Objective response by BICR



Subgroup analyses: PFS by BICR

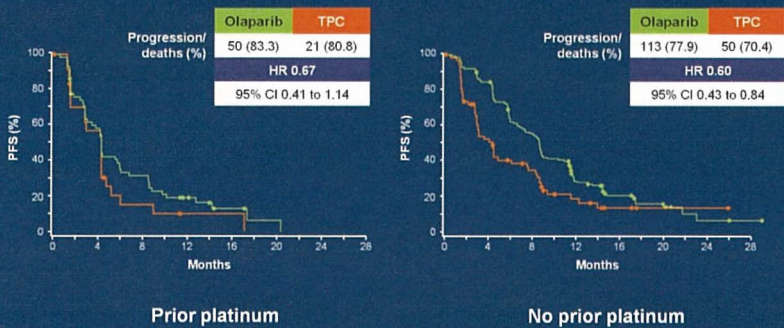


Safety summary: adverse events and exposure

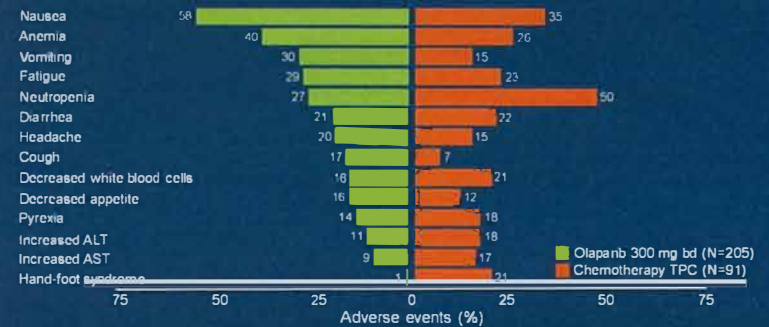
n (%)	Olaparib 300 mg bd (N=205)	Chemotherapy TPC (N=91*)
Grade 1-2	124 (60.5)	42 (46.2)
Grade ≥3	75 (36.6)	46 (50.5)
Death	1 (0.5)	1 (1.1)
AEs leading to drug discontinuations	10 (4.9)	7 (7.7)
AEs leading to dose reductions	52 (25.4)	28 (30.8)
AEs leading to dose interruptions/delay	72 (35.1)	25 (27.5)
Median duration of treatment, months	8.2 (0.5-28.7)	3.4 (0.7-23.0)

*6 patients did not receive study treatment and are not evaluable for safety

Subgroup analyses: PFS by BICR

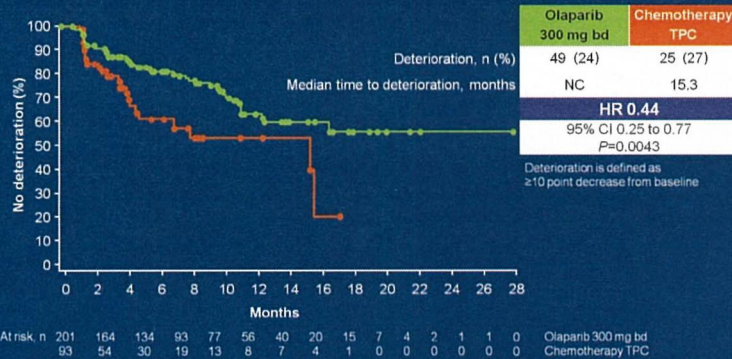


Adverse events (any grade) in ≥15% of patients



Irrespective of causality, MedDRA preferred terms for adverse events have been combined for 1) anemia and 2) neutropenia
ALT: alanine aminotransferase; AST: aspartate aminotransferase

Time to deterioration of global HRQoL



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Thank
You

jbalmana@vhio.net

Conclusions

- Olaparib tablet monotherapy provided a statistically significant and clinically meaningful PFS benefit versus standard-of-care chemotherapy for patients with HER2-negative metastatic breast cancer and a gBRCAm
- Olaparib was generally well tolerated with <5% discontinuing treatment for toxicity and a lower rate of Grade ≥ 3 AEs compared with chemotherapy
- OlympiAD is the first Phase III study in metastatic breast cancer patients demonstrating benefit for a PARP inhibitor over an active comparator

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Cancer genetic counselling and testing in view of treatment options/establishing new clinical pathways (Belgian experiences)

Tumor testing – where is its position in clinical pathways

Germline versus somatic mutations

GERM-LINE MUTATIONS

- Germline mutation
- Parental Gametes
- Embryo
- Entire organism carries the mutation
- Half of gametes carry mutation

SOMATIC MUTATIONS

- Somatic mutation
- Embryo
- Patch of affected area
- Organism
- Gametes of Offspring
- None of gametes carry mutation

2 hit hypothesis

Hereditary

Non-hereditary

BRCA1/2 germline mutations lead to increased ovarian cancer risk

BRCA1/2 somatic mutations are restricted to the neoplastic cells and may drive ovarian tumorigenesis in individuals without a germline mutation

Belgium: reimbursement since December 1st 2015

Hoofdstuk IV, nieuwe § 30n000
a) De specialiteit LYNPARZA komt voor vergoeding in aanmerking indien ze wordt toegediend als monotherapie voor de onderhuidse behandeling van volwassen patiënten met een BRCA-germuteerd platinagevoelig recidief hooggraadig serueus epitheliaal ovarium, tube- of primair peritoneaal carcinoom, die nog nooit behandeld zijn met olaparib of een andere PARP-inhibitor in een voorafgaande lijn.
De patiënte moet minstens 2 voorafgaande lijnen platina bevattende chemotherapie gekregen hebben en een volledige of partiële respons vertonen (volgens RECIST criteria) op de laatste gekregen platina bevattende chemotherapie en dat tot het einde van de chemotherapie.
Het interval tussen de voorlaatste lijn platina bevattende chemotherapie en ziekteprogressie bedroeg minstens 6 maanden.
De patiënte mag niet meer dan 8 weken voor de aanvang van de behandeling met LYNPARZA haar laatste lijn platina bevattende chemotherapie hebben voltooid.
Een BRCA mutatie (kernbaan en/of somatisch)

Therapy-orienting testing of BRCA1 and BRCA2 germline mutations in women with ovarian cancer

F. Claes, PhD, M. Duray, MD, PhD, M. Houben, MD, PhD, F. Wauters, MD, PhD, F. Frenkel, MD, PhD, J. Derom, MD, PhD, V. Beutels, MD, PhD

Key messages for clinical practice

- As positive test results do not only have implications for the patient but also for relatives, all patients should receive adequate pre- and post-test genetic counselling.
- Women with high-grade serous epithelial ovarian cancer and in good general condition (i.e. eligible for systemic treatment with low toxicity) should be eligible at any age for therapy-orienting germline BRCA1/2 testing.
- The request for germline BRCA1/2 testing should be made as soon as possible in the course of first-line treatment.
- For patients for whom the BRCA1/2 test results will have therapeutic implications, the turnaround time could be shortened if pre-test genetic counselling visits are organised in a collaborative effort between adequately trained clinical geneticists, and gynaecological and medical oncologists. The input of well-trained genetic counsellors, who would deal with counselling of all aspects of hereditary forms of breast/ovarian cancer, may be required in the future.
- Offering testing for germline BRCA1/2 mutations to all patients with high-grade serous epithelial ovarian cancer who are eligible for systemic treatment with low toxicity will lead to a limited increase in the number of requests for germline BRCA1/2 testing in the coming years in Belgium.

BeSHG guidelines for HBOC testing

- Woman with breast cancer + one or more of the following :
 - diagnosed ≤ 35 yrs
 - diagnosed < 50 yrs and one relative with bilateral, or ovarian, or breast < 50, or male breast cancer
 - bilateral breast cancer and both diagnosed < 50 yrs
 - ovarian cancer, any age
 - triple negative breast cancer < 50 yrs
 - three individuals with breast cancer, one is a first degree relative (FDR) of the other two (excluding male transmitters) and one diagnosed < 50 years
 - individual of ethnicity associated with higher frequency of specific mutations (eg, Ashkenazi Jewish): eligible for founder mutation testing
 - other family situations (eg multiple pancreatic cancer) with a priori chance of mutation >10% according to BRCAPro or Evans criteria or Manchester score
 - test more than one affected relative if criteria remain positive after excluding the negative case as a phenotype
- Woman with high grade serous or papillary epithelial ovarian cancer at any age (excludes borderline, low grade and mucinous ovarian cancer)
- Male with breast cancer
- Individual with pancreatic cancer at any age with ≥ 2 FDR excluding male transmitters with breast where one diagnosed
- Family history
 - First degree unaffected relative of any of the above on a case by case basis
 - Testing of unaffected family members should only be considered when no affected family member is available and then the unaffected family member with the highest probability of mutation should be tested



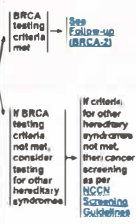
NCCN Guidelines Version 1.2018 BRCA-Related Breast and/or Ovarian Cancer Syndrome

NCCN Guidelines Index
 Table of Contents
 Discussion

BRCA1/2 TESTING CRITERIA^{1,2}

Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management. Testing of an individual without a cancer diagnosis should only be considered when an appropriate affected family member is unavailable for testing.

- Individual from a family with a known deleterious BRCA1/BRCA2 gene mutation
 - Personal history of breast cancer³ + one or more of the following:
 - Diagnosed ≤ 45 y
 - Diagnosed ≤ 50 y with:
 - An additional breast cancer primary⁴
 - ≥ 21 close blood relatives⁵ with breast cancer; at any age
 - ≥ 21 close relative with pancreatic cancer
 - ≥ 21 relative with prostate cancer (Gleason score ≥ 7 or metastatic)
 - An unknown or limited family history⁶
 - Diagnosed ≤ 50 y with:
 - Triple negative breast cancer
 - Diagnosed at any age with:
 - ≥ 22 close blood relatives with breast cancer, pancreatic cancer, or prostate cancer (Gleason score ≥ 7 or metastatic) at any age
 - ≥ 21 close blood relative⁵ with breast cancer diagnosed ≤ 50 y
 - ≥ 21 close blood relative⁵ with ovarian⁷ carcinoma
 - A close male blood relative⁸ with breast cancer
 - For an individual of ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish) no additional family history may be required
- Personal history of breast carcinoma³
 - Personal history of pancreatic carcinoma⁹
 - Personal history of prostate carcinoma¹⁰
- Personal history of metastatic prostate cancer (radiographic evidence of or biopsy-proven disease)
- Personal history of pancreatic cancer at any age with ≥ 21 close blood relative⁵ with ovarian carcinoma at any age or breast cancer ≤ 50 y or two relatives with breast, pancreatic cancer, or prostate cancer (Gleason score ≥ 7 or metastatic) at any age
- Personal history of metastatic prostate cancer (radiographic evidence of or biopsy-proven disease)
- Personal history of pancreatic cancer and Ashkenazi Jewish ancestry
- BRCA1/2 pathogenic mutation detected by tumor profiling on any tumor type in the absence of germline mutation analysis
- Family history only (significant limitations of interpreting test results for an unaffected individual should be discussed):
 - First- or second-degree blood⁵ relative meeting any of the above criteria
 - Third-degree blood⁵ relative who has breast cancer³ and/or ovarian⁷ carcinoma and who has ≥ 21 close blood relatives⁵ with breast cancer (at least one with breast cancer ≤ 50 y or breast/ovarian carcinoma)



¹ Personal history of breast carcinoma³
² Personal history of pancreatic carcinoma⁹
³ Personal history of prostate carcinoma¹⁰
⁴ An additional breast cancer primary⁴
⁵ ≥ 21 close blood relatives⁵ with breast cancer; at any age
⁶ An unknown or limited family history⁶
⁷ ≥ 21 close blood relative⁵ with ovarian⁷ carcinoma
⁸ A close male blood relative⁸ with breast cancer
⁹ Personal history of pancreatic carcinoma⁹
¹⁰ Personal history of prostate carcinoma¹⁰

Box 1. Criteria for Further Genetic Evaluation for Hereditary Breast and Ovarian Cancer¹⁰

- Women affected with one or more of the following have an increased likelihood of having an inherited predisposition to breast³ and/or ovarian, tubal, or peritoneal cancer and should receive genetic counseling and/or pre-symptomatic testing:
 - Epithelial ovarian, tubal, or peritoneal cancer
 - Breast cancer at age 45 years or less
 - Breast cancer and/or ovary/peritoneal with breast cancer at age 50 years or less or close relative⁵ with epithelial ovarian, tubal, or peritoneal cancer at any age
 - Breast cancer at age 50 years or less with a limited or unknown family history⁶
 - Breast cancer and have two or more close relatives⁵ with breast cancer at any age
 - Breast cancer and have two or more close relatives⁵ with pancreatic cancer or aggressive prostate cancer (Gleason score equal to or greater than 7)
 - Triple-negative breast cancer at age 60 years or less
 - Breast cancer and Ashkenazi Jewish ancestry at any age
 - Pancreatic cancer and have two or more close relatives⁵ with breast cancer; ovarian, tubal, or peritoneal cancer (Gleason score equal to or greater than 7)
 - Wormen unaffected with cancer, but with one or more of the following have an increased likelihood of having an inherited predisposition to breast and ovarian, tubal, or peritoneal cancer and should receive genetic counseling and be offered genetic testing:
 - A first-degree or several close relatives⁵ that meet one or more of the aforementioned criteria
 - A close relative⁵ carrying a known BRCA1 or BRCA2 mutation¹¹
 - A close relative⁵ with male breast cancer



The American College of Obstetricians and Gynecologists
 www.acog.org



ACOG PRACTICE BULLETIN

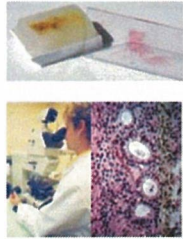
Clinical Management Guidelines for Obstetrician-Gynecologists

NUMBER 182, SEPTEMBER 2017 (Replaces Practice Bulletin Number 103, April 2009)

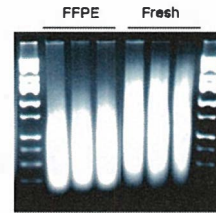
Co-Chair: Practice Bulletin-Genetics, Committee on Genetic Testing, The Practice Bulletin was developed by the American College of Obstetricians and Gynecologists' Committee on Practice Bulletin-Obstetrics and Committee on Genetics in collaboration with Susan C. Holcomb, MD, and Karen Lu, MD, and the Society of Obstetrician-Gynecology in collaboration with Lawrence Chen, MD and C. Brian Powell, MD

Hereditary Breast and Ovarian Cancer Syndrome

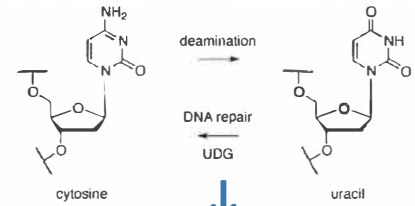
tBRCA testing - workflow



FFPE: caveats



Fragmentation of DNA



artificial C:G > T:A SNVs

1



>20% tumor cells

Time between resection and fixation: <1h

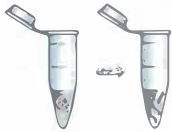
Fixation time: 6-72h
10% formaline

2



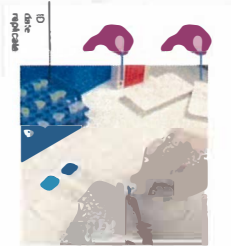
4-6 slides
10 μ M

4



DNA

tumor region: 5x5 mm



3

5



Multiplex PCR

6



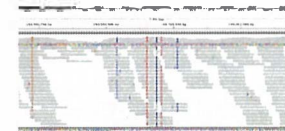
Library preparation

9



report

8

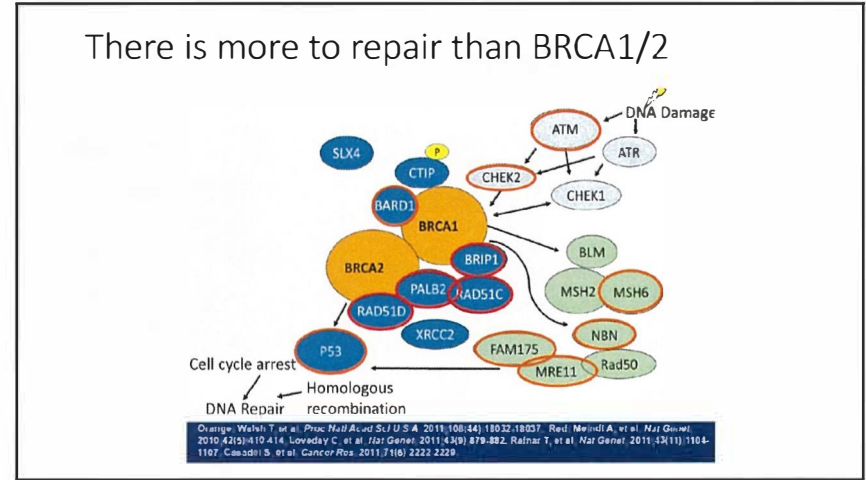
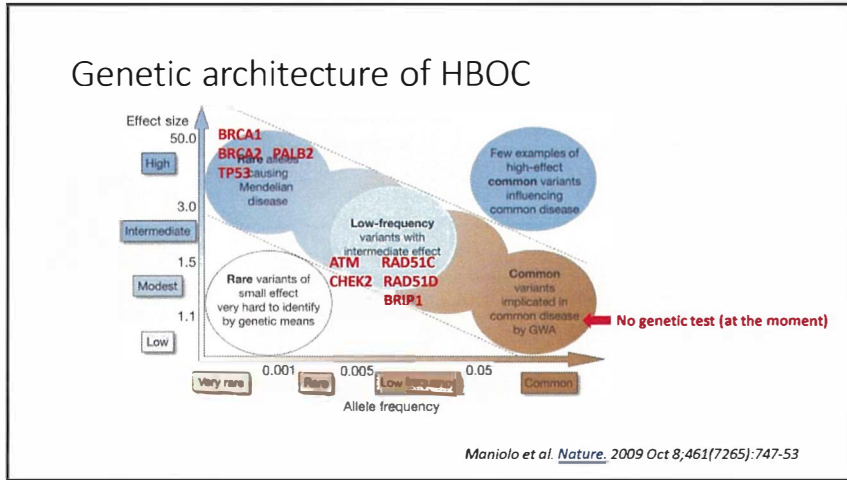
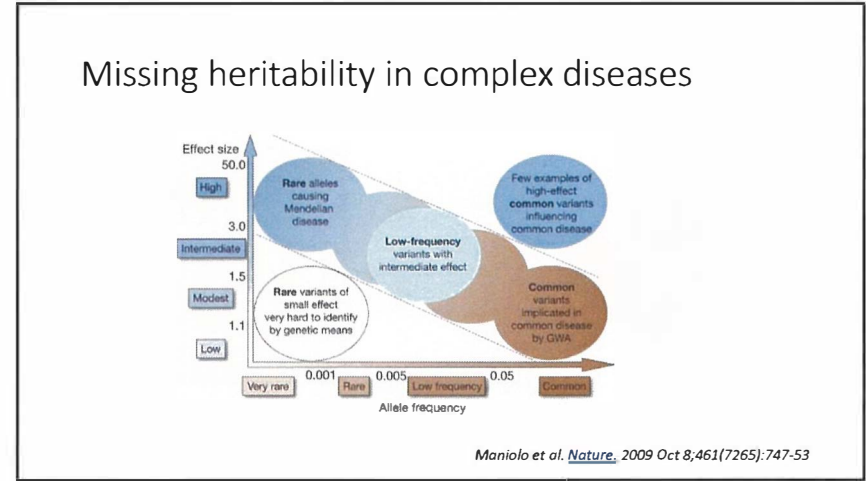
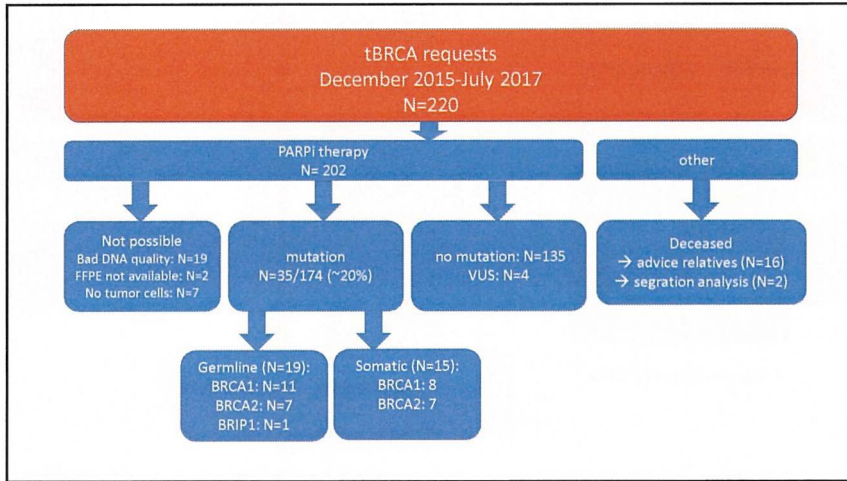


data analysis

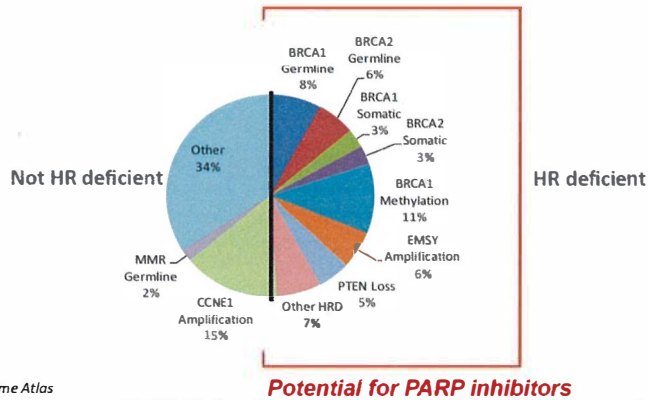
7



sequencing



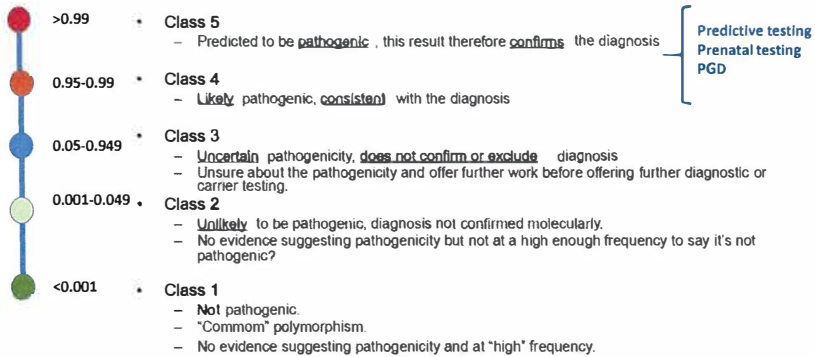
Homologous recombination deficiency



Variant classification

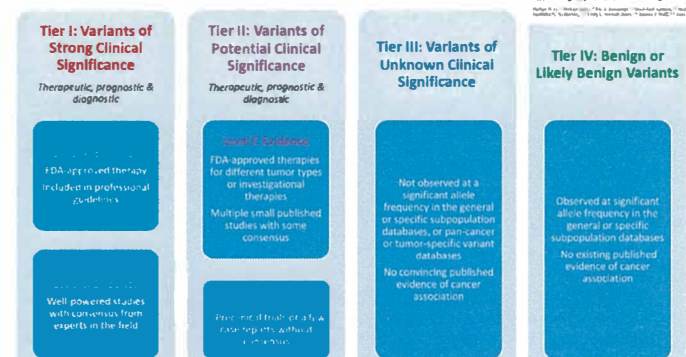
Purpose	Type of variant (source of DNA)	Classification recommendations
Cancer risk assessment of a person + relatives; PGD/PND	Germline (blood)	5-tier IARC/ACMG (1)
Clinical actionability: diagnosis, prognosis, treatment	Somatic (tumor)	5-tier (2, 3, 4) vs. 4-tier (5)

Variant classification – genetics: 5 classes



Classes 3, 4, 5 are reported

Variant classification – precision medicine: 4 tier system



Tiers I to III must be reported; it is NOT recommended to include tier IV variants/alterations in the report

Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer
 A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists

Variant classification – precision medicine: 5 tier system

Classification methods for somatic cancer variants			
Classification*	SVC method [21**]	PHIAL method [22**]	BWH/DFCI method
Class 1	Clinically actionable for therapeutic, prognostic, or diagnostic purposes for same tumor type	Validated therapeutic, prognostic, or diagnostic implications for same tumor type	Validated therapeutic, prognostic, or diagnostic implications for same tumor type
Class 2	Clinically actionable for therapeutic, prognostic, or diagnostic purposes for a different tumor type	Limited evidence of therapeutic, prognostic, or diagnostic implications for same tumor type	Validated therapeutic implications for a different tumor type, or limited evidence of prognostic or diagnostic implications for same tumor type
Class 3	Other variants in this gene in this primary tumor are established as actionable for same tumor type	Clinical evidence of therapeutic response from another tumor type	Preclinical or inferential therapeutic, prognostic, or diagnostic implications
Class 4	Other variants in this gene in this primary tumor are established as actionable for a different tumor type	Preclinical association to therapeutic response	Novel or unstudied in cancer
Class 5	(A) Gene is not actionable for any tumor type (B) Established as benign	Inferential association to therapeutic response	Established as benign

BWH/DFCI = Brigham Women's Institute/Dana Ferber Cancer Institute.

* PHIAL method classifications referred to as Levels A-E, while other methods refer to as Tiers.

Hoskinson et al, Current Opinion in Genetics and Development, 2017

Tumor first? Germline first?

- Discuss advantages and disadvantages

Illustrative examples

KORAK NAPREJ pri zdravljenju onkoloških bolnikov.



HBOC – germline/ somatic genetic testing – laboratory experiences (latest updates)

Srdjan Novaković

Hereditary breast and ovarian cancer - HBOC

- Five to ten percent of all breast/ovarian cancers (HBOC) are inherited, primarily due to mutations in *BRCA1* or *BRCA2* genes.
- The rest of HBOC hereditary cancers are a result of mutations in other genes such as *TP53*, *STK11*, *PTEN*, *CDH1*, *MSH2*, *MLH1*, *MSH6*, *PMS2*, *EPCAM*, *CHEK2*, *PALB2*, *ATM*, *RAD51c*, *BLM*, *BRIP1*, *RAD51D*, *NBN*, *NF1*, *BARD1*, *MRE11A*, *XRCC2*, *ABRAXAS*, *CYP11A1*, *CYP17*, *GSTP* or others.

S. NOVAKOVIĆ

BRCA1 and BRCA2

Since the identification and cloning of *BRCA1/2* genes, according to ClinVar data base, more than 5000 different pathogenic or likely pathogenic mutations have been discovered, most of them in only one or few families.

S. NOVAKOVIĆ

BRCA1 and BRCA2 Mutation Carriers

ABSTRACT The identification of *BRCA1* and *BRCA2* mutation carriers... *BRCA1* carriers have a lifetime risk of breast cancer of 65% and ovarian cancer of 39%. *BRCA2* carriers have a lifetime risk of breast cancer of 69% and ovarian cancer of 24%. The risk of contralateral breast cancer is 42% for *BRCA1* and 35% for *BRCA2* carriers.

KEY WORDS: BRCA1, BRCA2, breast cancer, ovarian cancer, contralateral breast cancer, mutation carriers, lifetime risk, cumulative incidence, penetrance, penetrance curves, Kaplan-Meier survival analysis, logistic regression, multivariate analysis, hazard ratios, confidence intervals, p-values, significance levels, statistical significance, multivariate analysis, hazard ratios, confidence intervals, p-values, significance levels, statistical significance.

INTRODUCTION The identification of *BRCA1* and *BRCA2* mutation carriers... *BRCA1* carriers have a lifetime risk of breast cancer of 65% and ovarian cancer of 39%. *BRCA2* carriers have a lifetime risk of breast cancer of 69% and ovarian cancer of 24%. The risk of contralateral breast cancer is 42% for *BRCA1* and 35% for *BRCA2* carriers.

CONCLUSIONS The identification of *BRCA1* and *BRCA2* mutation carriers... *BRCA1* carriers have a lifetime risk of breast cancer of 65% and ovarian cancer of 39%. *BRCA2* carriers have a lifetime risk of breast cancer of 69% and ovarian cancer of 24%. The risk of contralateral breast cancer is 42% for *BRCA1* and 35% for *BRCA2* carriers.

S. NOVAKOVIĆ

BRCA 1/2 testing criteria



NCCN Guidelines Version 2.2017

BRCA-Related Breast and/or Ovarian Cancer Syndrome

NCCN Guidelines Index
Table of Contents

BRCA 1/2 TESTING CRITERIA^{1,2}

Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and other genetic testing and management. Testing of an individual without a cancer diagnosis should only be considered when an appropriate affected family member is unavailable for testing.

- Individual from a family with a known deleterious BRCA1/BRCA2 gene mutation
- Personal history of breast cancer³ + one or more of the following:
 - Diagnosed ≤ 45 y
 - Diagnosed ≤ 50 y with:
 - An additional breast cancer primary⁴
 - ≥ 2 close blood relatives⁵ with breast cancer at any age
 - ≥ 2 close relatives with pancreatic cancer
 - ≥ 2 relatives with prostate cancer (Gleason score ≥ 7)
 - An unknown or limited family history⁶
- Diagnosed ≤ 50 y with:
 - Triple negative breast cancer
 - Diagnosed at any age with:
 - ≥ 2 close blood relatives with breast cancer, pancreatic cancer, or prostate cancer (Gleason score ≥ 7) at any age
 - ≥ 2 close blood relatives⁵ with breast cancer diagnosed ≤ 50 y
 - ≥ 2 close blood relatives⁵ with ovarian⁷ carcinoma
 - A close male blood relative⁸ with breast cancer
- For an individual of ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish), no additional family history may be required⁹
- Personal history of ovarian¹⁰ carcinoma
- Personal history of male breast cancer

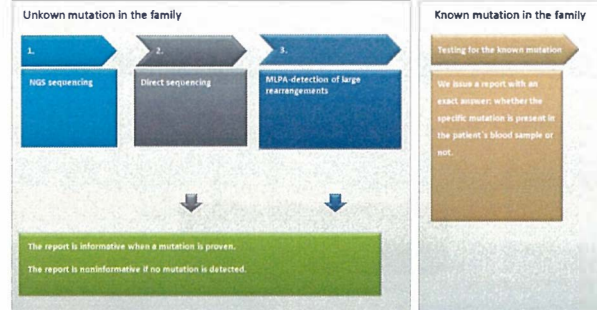
BRCA testing criteria met

See Evidence-based (BRCA)

If criteria for other hereditary syndromes not met, consider testing for other hereditary syndromes

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BRCA1 and BRCA2 screening strategy

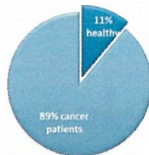


S. NOVAKOVIČ

Results of BRCA1/2 mutation screening 1999 - december 2016

3071 tested individuals from 2095 Slovene breast and/or ovarian cancer families

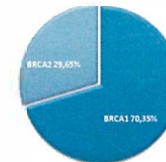
Ratio of healthy and diseased probands among the first tested family members



S. NOVAKOVIČ

Results of BRCA1/2 mutation screening 1999 – december 2016

- 452 BRCA1/2 positive families
 - BRCA1 – 318
 - BRCA2 – 134



- Mutation detection rate: 21.6% (452/2095)

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BRCA 1/2 mutation spectrum 1999 - december 2016

94 different deleterious mutations:

43 in *BRCA1*

- missense mutations affecting the 5'RING domain
- nonsense mutations
- frame-shift mutations
- deletions of whole exons
- splice site mutations

51 in *BRCA2*

- splice site mutations
- nonsense mutations
- frame-shift mutations

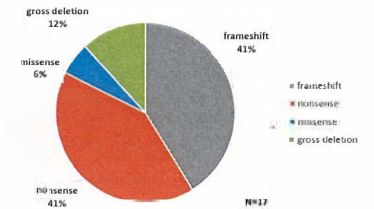
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Novel mutations - pathogenic variants in *BRCA1* and *BRCA2*

In the period from 1999 to 2016

gene	cHGVS	pHGVS
<i>BRCA1</i>	c.121dupC	p.(His41Profs*25)
	c.181T>A	p.(Cys61Ser)
	c.457_458delAG	p.(Ser153Cysfs*5)
	c.1193C>A	p.(Ser398*)
	c.4356delA	p.(Ala1453Glnfs*3)
	c.5377A>T	p.(Lys1793*)
<i>BRCA2</i>	c.775A>T	p.(Arg259*)
	c.5101C>T	p.(Gln1701*)
	c.5291C>G	p.(Ser1764*)
	c.5433_5436delGGAA	p.(Glu1811Aspfs*3)
	c.6100delinsTA	p.(Arg2034*)
	c.6421_6424dupGGTT	p.(Ser2142Trpfs*6)
	c.6491_6494delAGTT	p.(Gln2164Argfs*3)
	c.7303C>T	p.(Gln2435*)
c.8808delG	p.(Asn2937Metfs*39)	

Novel *BRCA1* and *BRCA2* mutations



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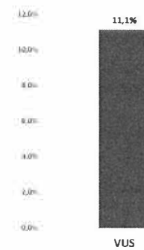
BRCA 1/2 mutation spectrum 1999 - december 2016

- The most common mutation found in the *BRCA1* gene was missense mutation c.181T > G (p.Cys61Gly). It was detected in 82 families.
- The most common mutation in the *BRCA2* gene was a splice site mutation c.7806-2A > G. It was detected in 33 families.

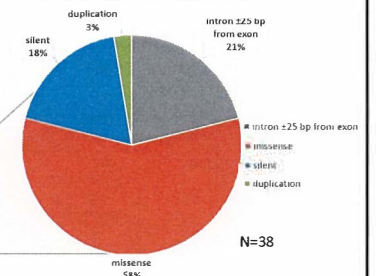
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BRCA1 and *BRCA2* - variants of uncertain significance (VUS)

% patients harbouring VUS in *BRCA1* and *BRCA2*



novel *BRCA1* and *BRCA2* VUS



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NGS - genes tested in breast and ovarian cancer patients in 2015 - 2016

NGS panel 2015:

ATM, BRCA1, BRCA2, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, PTEN, STK11, TP53

NGS panel 2016:

ATM, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, NF1, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, TP53

Number of patients with different mutations detected with NGS in 2015 - 2016

BRCA1	BRCA2	TP53	STK11	PTEN	CDH1	MSH2	MLH1	MSH6	PMS2	EPCAM	CHEK2	PALB2	ATM	BRIP1	NF1	NBN	RAD51C	RAD51D
116	56	1	2	0	1	1	2	14	11	11	1	1	1	3	4	1		

* in a single patient mutations in both BRCA2 and in ATM were detected simultaneously

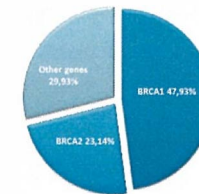
Reported incidental findings

SMARCA4	FH	BLM	FLCN	XPA	SLX	MUTYH
1	3	1	1	1	1	3

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Distribution of mutations detected with NGS in breast and ovarian cancer patients in 2015 - 2016

Mutation detection rate in 2015 - 2016: 28,70%



S. NOVAKOVIČ

BRCA1/2 mutations in ovarian cancer patients in the period 2012-2016

Most ovarian cancer patients have been tested for germline BRCA mutations
Only lately have we begun to offer testing of somatic BRCA mutations

Patients carrying germline or somatic BRCA mutation have been associated with a better prognosis as well as better response to platinum-based therapy and PARP inhibitors

Altogether 302 tested ovarian cancer patients
Mutations detected in 31,79% of cases

GENE	No. of patients with mutation	%	No. Of different mutations
BRCA1	76	79,17%	28
BRCA2	20	20,83%	16
BRCA1/2	96	100%	44

S. NOVAKOVIČ

Conclusion

Even though the testing focus in HBOC families is on detection of BRCA mutations, other highly penetrant, but less frequently mutated genes, have been recommended for testing

Genetic testing of BRCA genes provides the key to:

- Accurate cancer risk assessment
- Effective genetic counseling
- Appropriate medical follow-up
- Appropriate treatment
 - DNA quality from FFPE tissue is a major obstacle
 - Improve analysis and interpretation by:
 - Running in duplicate
 - being careful with assay design and minimum coverage
 - Additional steps (e.g. Uracil-DNA Glycosylase (UDG) treatment) can help minimise deamination artefacts

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ONKOLOŠKI
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OF ONCOLOGY
LJUBLJANA



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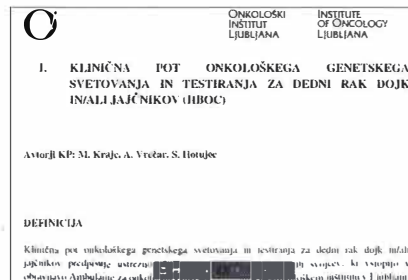
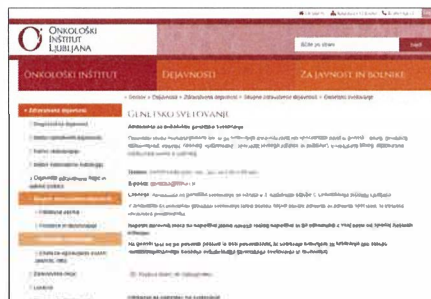
Cancer genetic counselling – new clinical pathways in view of treatment options

Ana Blatnik, Mateja Krajc, Ksenija Strojnik



HBOC at the Institute of Oncology

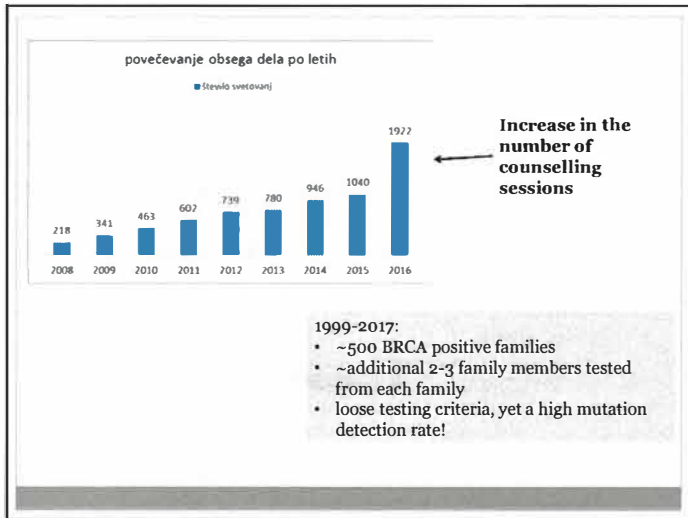
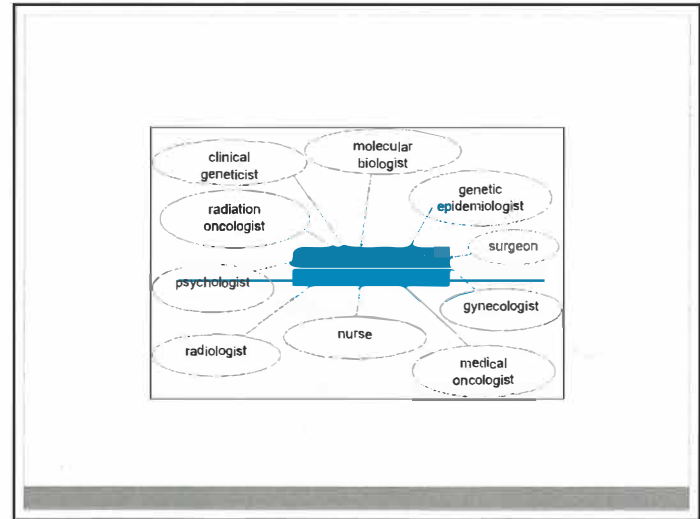
- 1999 - genetic testing for *BRCA* genes available - in collaboration with Vrije Universiteit Brussel
- 2008 - all tests performed at the Institute of Oncology Ljubljana, state insurance covers the costs of counseling and testing when indicated
- 2010 –management of individuals at high risk for breast/ovarian cancer at our institution
- 2011 – clinical pathways established
- 2014/2015 – genetic testing performed using an NGS based approach (multi-gene panel)
- **2014 – priority assessment for therapeutical purposes introduced**



All cancer diagnosis verified in the Cancer registry of the Republic of Slovenia - one of the oldest population based cancer registry in Europe (established in 1950)

Probabilities for carrying a mutation and identifying breast/ovarian cancer carriers using various predictive programmes (Maga-Cancer, BRACANCA...)

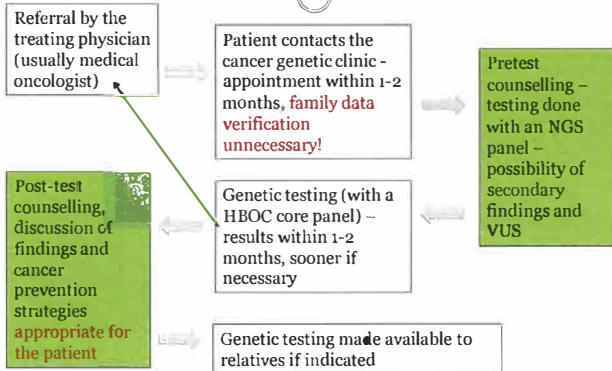
Genetic testing and management/surveillance programs for high-risk individuals in accordance with NCCN guidelines



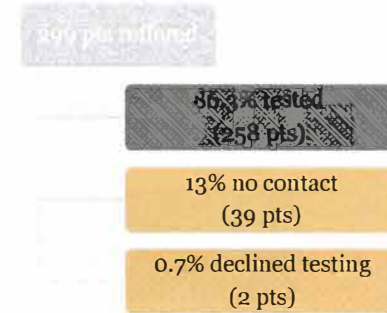
Olaparib as a game changer!

- PARP inhibitor olaparib approved for *BRCA* mutation carriers as maintenance therapy in recurrent platinum sensitive OC
- in October 2014 we started offering *BRCA* tests to all ovarian cancer, fallopian tube and primary peritoneal serous carcinoma patients with high grade serous histology
- need for fast-tracking - how to manage the additional workload?

Simplifying the clinical pathway

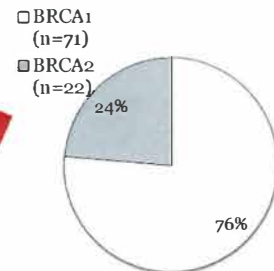


Attendance rate



BRCA mutation detection rate

Mutation status	No of pts (258)	%
None identified	150	58.1%
BRCA 1/2	93	36.0%
other*	15	5.8%



*other genes from Illumina TruSight Cancer sequencing panel

Other findings

Mutation identified	No of pts (258)	%
None	150	58.1%
BRCA1/2	93	36.0%
other*	15	5.8%

*Other gene mutations identified from the panel	No of pts (n=15)
ATM	4
RAD51C	3
RAD51D	1
MUTYH	2
CHECK2	1
MSH2	1
PALB2	1
CDH1	1
STK11	1

Mutation detection rate depending on family history

Positive family history:
165 pts (64%)

• BRCA 1/2 mutation detection rate: **44.8%**
(74/165 pts)

Negative family history:
93 pts (36%)

• BRCA 1/2 mutation detection rate: **18.3%**
(17/93 pts)

Mutation rate in patients tested when diagnosed with ovarian cancer

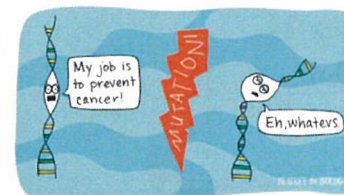
BRCA 1/2 mutation detection rate in 134 pts tested at the time of OC diagnosis

Excluding patients with recurrent OC or a long disease-free interval

33.6%
(45/134 pts)

Conclusions

- Testing all high-grade serous OC yielded an unusually **high mutation detection rate** – a higher prevalence of mutation carriers in the Slovene population or a selection bias?
- Panel testing (VUS, secondary findings, mutations in OC genes with no therapeutic implications)
- Adopting a modified strategy of germline testing with patients attending a cancer genetics clinic feasible for OC, but with breast cancer...
- Tumor tissue genetic testing – **pros** and **cons** (detecting somatic mutations vs more limited panels)?
- Testing for defective homologous repair?




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klinični center
Maribor

Slovenian experiences with olaparib in ovarian cancer treatment

Maja Ravnik, Erik Škof

What's new in the management of BRCA positive ovarian and breast cancer patients- 2nd conference
19th of October 2017


Ovarian cancer: Slovenija




- Incidence – 177*
- Median age – 60 years
- Stage of disease:
 - 75% advanced (FIGO III/IV)
- Histology
 - „High-grade“ serous (75%),
- Frequent relapses (80%)
- 5 y OS in SLO 43%*

* Cancer in Slovenia 2013

Ovarian cancer: Slovenija




- Study 19
 - showed 7 months PFS* benefit of maintenance therapy with olaparib in patients with relapsed BRCA+ ovarian cancer¹.
 - Olaparib prolonged overall survival for 4,7 months compared to placebo ² (the difference was not statistically significant).
- EMA approval of olaparib for relapsed BRCA+ ovarian cancer on 16/12/2014
- Since **5th of february 2016** olaparib therapy is reimbursed by ZZZS (Health Insurance Institute of Slovenia) for patients with relapsed BRCA+ ovarian cancer in Slovenia



 PFS* – progression-free survival

1. Ledermann J et al, Lancet Oncol 2014
 2. Ledermann J et al, Lancet Oncol 2016

Ovarian cancer: Slovenija



- Since september 2014:
 - All patients with HGS* cancer of ovaries, fallopian tubes or PPSC are offered to perform BRCA genetic testing at **diagnosis**
 - The aim of BRCA genetic testing is:
 - **treatment with olaparib**
 - prevention of breast and ovarian cancer
 - Active search for BRCA+ patients
 - confidential data
 - multidisciplinary genetic consilium


 HGS* - high-grade serous

Slovenian guidelines for treatment of ovarian cancer 2014/15

Olaparib experience in Slovenija



- Systemic therapy is applied in two Institutions:
 - Institute of Oncology Ljubljana
 - University Medical centre Maribor
- No clinical trial with olaparib in Slovenia
- First 2 pts received olaparib through „Early-access programme“ in November 2015.
- Label for olaparib is the same as in Study 19.

Ovarian cancer: Slovenija



- Current recommendations:
 - The „need for speed“ of gBRCA testing results:
 - Medical oncologist → recommends genetic counseling
 - Geneticist → pretest counseling + blood sample
 - Molecular lab → blood testing results
 - Geneticist → posttest counseling
 - Medical oncologist → therapy with olaparib
 - Waiting list for genetic counseling
 - „Highest-priority“ patients with relapsed HGS** ovarian cancer
 - „High-priority“ patients with HGS at diagnosis
- Near future – upfront tBRCA* testing ?
 - Faster results
 - Complete results – tBRCA = sBRCA+gBRCA
 - No need for genetic counselling in majority (pts. and relatives)

<3 months

Olaparib experience in Slovenija



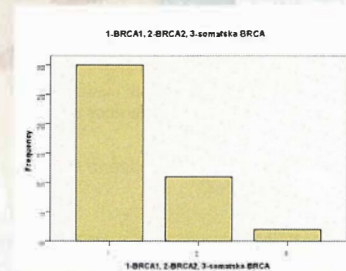
- Overall 48 pts received therapy with olaparib
 - At the moment: 25 pts on treatment
 - Duration of th: range 1-23 months (median 5 months)
 - AE – mild nausea, fatigue, anemia (G1)
 - 12 pts. had progression of the disease
 - 4 pts SAE – G3 anemia
 - 2pts continue th with reduced dose (50% dose)
 - 2 pts declined th. without evidence of AE

Olaparib experience in Slovenija (data from Institute of Oncology Ljubljana)



- Median age - 60 years
 - BRCA 1 – 56 years
 - BRCA 2 – 63 years
- BRCA 1 – 70%

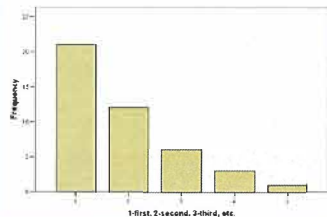
1-BRCA1, 2-BRCA2, 3-somatika BRCA				
Valid	Frequency	Percent	Valid Percent	Cumulative Percent
1	30	69.8	69.8	69.8
2	11	25.6	25.6	95.3
3	2	4.7	4.7	100.0
Total	43	100.0	100.0	



Olaparib experience in Slovenija (data from Institute of Oncology Ljubljana)



Number of relapses prior to olaparib therapy



1-prvi, 2-drugi, 3-treći				
	Frequency	Percent	Valid Percent	Cumulative Percent
Valid 1	21	46.9	46.9	46.9
2	12	27.9	27.9	74.8
3	6	14.0	14.0	90.7
4	3	7.0	7.0	97.7
5	1	2.3	2.3	100.0
Total	43	100.0	100.0	

Olaparib experience in Slovenija (data from Institute of Oncology Ljubljana)



Adverse events of olaparib:

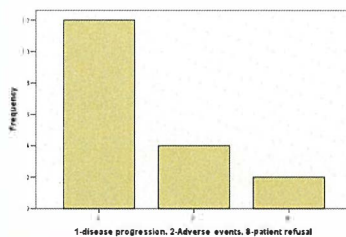
- Nausea
 - usually first month (metoclopramid p.p.)
- Fatigue
 - in majority first month (? KT)
- Anemia
 - in majority G1 (no transfusion needed)
 - G3 (Hb <80g/l) – 4 patients
 - 2 patients continue with dose reduction (50%) – G1 anemia – still on therapy
 - 1 patient with dose reduction (50%) had disease progression – end of therapy
 - 1 patient despite dose reduction (50%) persistent G3 anemia – end of therapy due to SAE

1-nausea, 2-fatigue, 3-anemia, ... 12-nausea and fatigue...				
	Frequency	Percent	Valid Percent	Cumulative Percent
Valid 0	4	9.3	9.3	9.3
1	6	14.0	14.0	23.3
2	3	7.0	7.0	30.2
3	20	46.5	46.5	76.7
13	1	2.3	2.3	79.1
123	9	20.9	20.9	100.0
Total	43	100.0	100.0	

Olaparib experience in Slovenija (data from Institute of Oncology Ljubljana)



Reasons for discontinuation of olaparib



1-progres, 2-NE, 3-otkaz				
	Frequency	Percent	Valid Percent	Cumulative Percent
Valid 1	12	66.7	66.7	66.7
2	4	22.2	22.2	88.9
3	2	11.1	11.1	100.0
Total	18	100.0	100.0	

17/21 patients with 1 relapse are still on therapy
SAE – G3 anemia (despite dose reduction)

Genetic counseling – information for patients

KONTAKT:

OBEDIKO ALI PO TELEFONU:
01 5079 140 (pov. vs. jpt), od 8. do 18. ure

PO E-POŠTO:
genetik@ukc-lj.si

Olaparib – information for patients



Thank you !



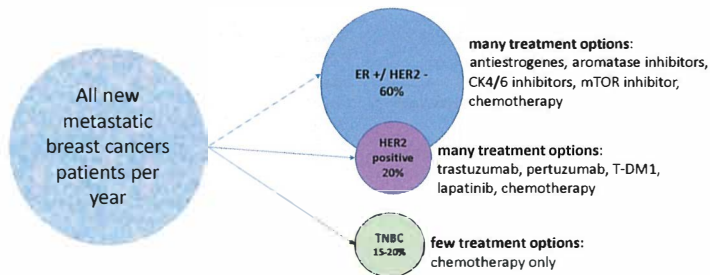
PARP inhibitors in breast cancer – current and future perspectives in Slovenia

Simona Borštnar
 Division of Medical Oncology
 Institute of oncology Ljubljana

Questions

- What is the proportion of metastatic breast cancer patients suitable for treatment with PARP inhibitors?
- What is current approach in the treatment of BRCA mutation carriers?
- When PARP inhibitors will be available for the treatment of patients with breast cancer in Slovenia?
- Are we ready to use PARP inhibitors in breast cancer?

Clinical Breast Cancer Subsets Defined by IHC in metastatic disease



Overall survival of patients with metastatic breast cancer (2008–2013)

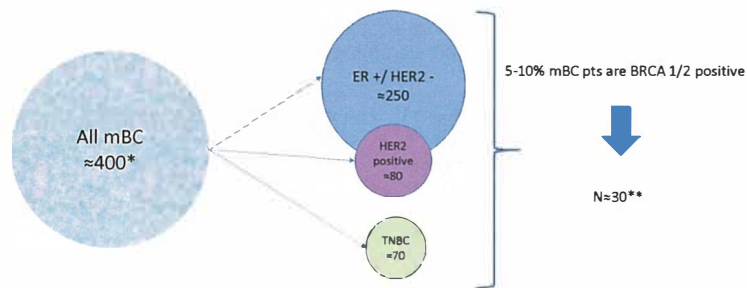
Breast cancer subtype	2008	2009	2010	2011	2012	2013
HR+/HER2- (n = 9908)	43.7 (40.2–46.6)	42.0 (38.9–44.6)	40.9 (38.0–43.4)	42.0 (39.26–45.04)	44.5 (41.8–47.3)	40.3 (37.8–NR)
HER2 +++ (n = 2861)	38.67 (33.6–44.6)	42.3 (38.3–50.8)	40.1 (35.2–45.6)	42.38 (36.5–49.8)	51.1 (46.5–NR)	Median NR
HR-/HER2- (n = 2317)	15.1 (12.7–16.4)	15.1 (13.0–17.4)	14.7 (13.2–17.0)	14.0 (11.4–15.9)	13.9 (11.4–15.9)	14.1 (12.5–15.5)

new therapies are needed

HR, hormone receptor; NR = not reached

Delaloge S, *et al* ASCO 2017 (Abstract 1078).

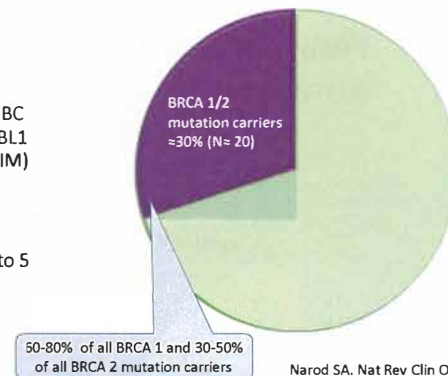
Estimated number of metastatic breast cancer (mBC) patients according to different subtypes in Slovenia



* Estimated number of new mBC per year: primary metastatic (N =90) and secondary metastatic (N =300-320)
** estimated number of BRCA positive mBC per year

Characteristics of TNBC

- Most TNBC are invasive ductal, minority represent medullary, metaplastic or adenoid cystic carcinoma.
- By gene expression profiling TNBC are classified in two basal-like (BL1 and BL2), immunomodulatory (IM) and luminal androgen receptor (LAR) subtype.
- Distant metastatic recurrences tend to occur within the first 2 to 5 years after diagnosis, late recurrences are rare.



Narod SA. Nat Rev Clin Oncol 2010

Current treatment in BRCA positive breast cancer patients

- Traditionally, BRCA carriers have received conventional systemic chemotherapy based on their baseline tumor characteristics.
- Tumors arising in patients with BRCA mutations were shown to be particularly sensitive to platinum compounds or inhibitors of PARPs.
- BRCA1-mutation carriers seem to benefit from anthracycline-taxane-containing regimens as much as sporadic triple-negative breast cancers do.

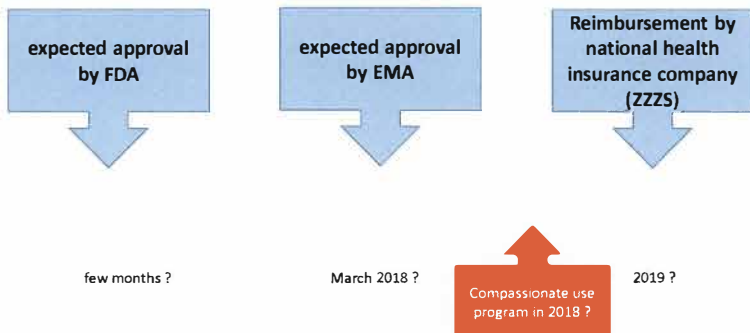
Sikov WM et al. JCO 2015; Rugo HS et al. NEJM 2016; von Minckwitz G et al. Lancet Onc. 2014

Clinical studies with PARPs in BRCA1/2 positive advanced breast cancer

Study name	PHASE	INVESTIGATIONAL ARM	COMPARATOR ARM	PRIMARY ENDPOINT
OlympiAD	3	olaparib	Physician choice ChT	PFS COMPLETED
BROCADE	2	veliparib+ temozolamide or carbo/pacli	Placebo+ Carbo/pacli	PFS
NCT02163694	3	veliparib+ carbo/pacli	placebo+ carbo/pacli	PFS
EMBRACA	3	tazaloparib	Physician choice ChT	PFS
ABRAZO	2	tazaloparib	Single arm study	ORR
BRAVO	3	niraparib	Physician choice ChT	PFS
NCT00664781	2	Rucaparib+ cisplatin	Cisplatin	ORR, safety

Livraghi L and Garber JE. MC Medicine 2015; 13:188

When PARP inhibitors will be available for the treatment of patients with breast cancer in Slovenia?



Are we ready to use PARP inhibitors for breast cancer in Slovenia?

Genetic testing is available to all breast cancer patients who meet the criteria:

- a family member with BRCA mutation
- diagnosis of BC under the age of 45
- diagnosis of TNBC under the age of 60
- diagnosis of two separate breast cancers (one of which was diagnosed under the age of 50)
- diagnosis of breast cancer and ovarian cancer in same person
- diagnosis of ovarian cancer
- man with breast cancer
- one or more close blood relatives with breast cancer that was diagnosed under the age of 50

It is very likely that we will have information about the BRCA mutation in majority of patients at the time of relapse.

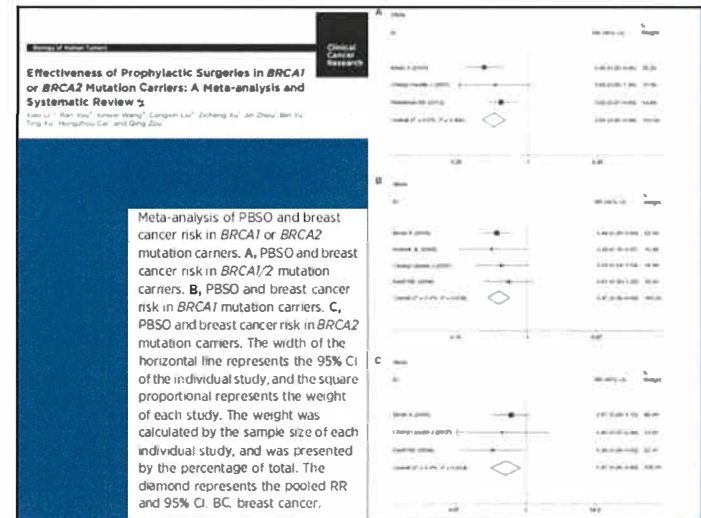
Surgical treatment of BRCA positive breast cancer patients – current practice and Slovenian results

Janez Zgajnar
Institute of Oncology Ljubljana

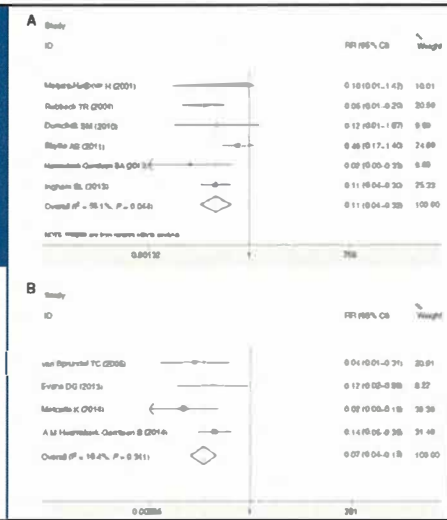
All data presented are unpublished

Strategies in BRCA1/2 mutation carriers

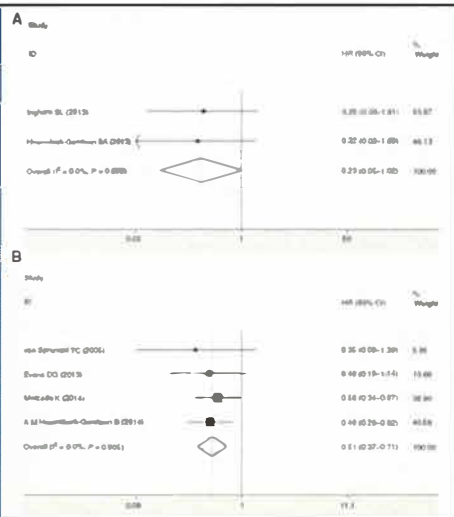
- Intensive follow up
- Chemoprevention – (tamoxifen)
- Prophylactic surgery
 - Oophorectomy
 - Mastectomy



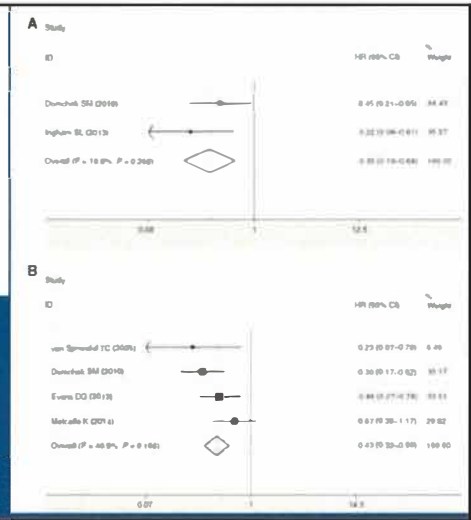
Meta-analysis of PM and breast cancer risk in *BRCA1/2* mutation carriers. **A**, BPM and breast cancer risk in *BRCA1/2* mutation carriers. **B**, CPM and CBC risk in *BRCA1/2* mutation carriers. The width of the horizontal line represents the 95% CI of the individual study, and the square proportional represents the weight of each study. The weight was calculated by the sample size of each individual study, and was presented by percentage of total. The diamond represents the pooled RR and 95% CI. BC, breast cancer.



Meta-analysis of PM and all-cause mortality in *BRCA1/2* mutation carriers. **A**, BPM and all-cause mortality in *BRCA1/2* mutation carriers with no breast cancer. **B**, CPM and all-cause mortality in *BRCA1/2* mutation carriers with uBC. The width of the horizontal line represents the 95% CI of the individual study, and the square proportional represents the weight of each study. The weight was calculated by the sample size of each individual study, and was presented by the percentage of total. The diamond represents the pooled RR and 95% CI. BC, breast cancer.



Meta-analysis of PBSO and all-cause mortality in *BRCA1/2* mutation carriers. **A**, PBSO and all-cause mortality in *BRCA1/2* mutation carriers with no prior history of breast cancer. **B**, PBSO and all-cause mortality in *BRCA1/2* mutation carriers with prior history of breast cancer. The width of the horizontal line represents the 95% CI of the individual study, and the square proportional represents the weight of each study. The weight was calculated by the sample size of each individual study, and was presented by the percentage of total. The diamond represents the pooled RR and 95% CI. BC, breast cancer.

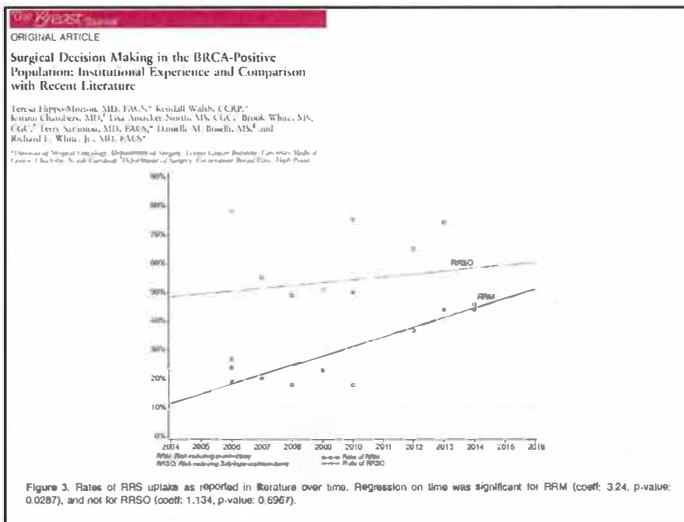


Original Article
Surgical Decision Making in the BRCA-Positive Population: Institutional Experience and Comparison with Recent Literature
 Teresa J. Hippert-Morris, MD, FACS,* Kendall W. Jahn, CCRP,*
 Kaitlyn O. Blandford, MEd,† Eric Simonsick, MEd, MEd,† G. Lee Smith, White, MS,
 PhD,† Terry Sarantis, MD, FACS,† Daniela M. Brucoli, MD,† and
 Richard L. White, Jr., MD, FACS*

Table 2. Reported Rates of Uptake of RRS in the BRCA-Positive Population in Current Literature

Author	Date	Sample size	% RRM	% Surveillance	% RRSO
Uysal et al.	2006	37	24	57	27
Kranz et al.	2006	43	19	NR	78
Friebe et al.	2007	537	21	38	55
Metcalf et al.	2008	1,383	18	NR	49
Beattie et al.	2009	272	23	NR	51
Kwong et al.	2010	31	18	82	18
Skytte et al.	2010	306	50	NR	75
Schwartz et al.	2012	144	37	NR	85
Garcia et al.	2013	305	44	NR	74
Fhippo et al.	2014	87	44	41	46

NR, not reported; RRS, risk-reducing surgery; RRM, risk-reducing mastectomy; RRSO, risk-reducing salpingo-oophorectomy.



RESULTS OF THE INSTITUTE OF ONCOLOGY LJUBLJANA

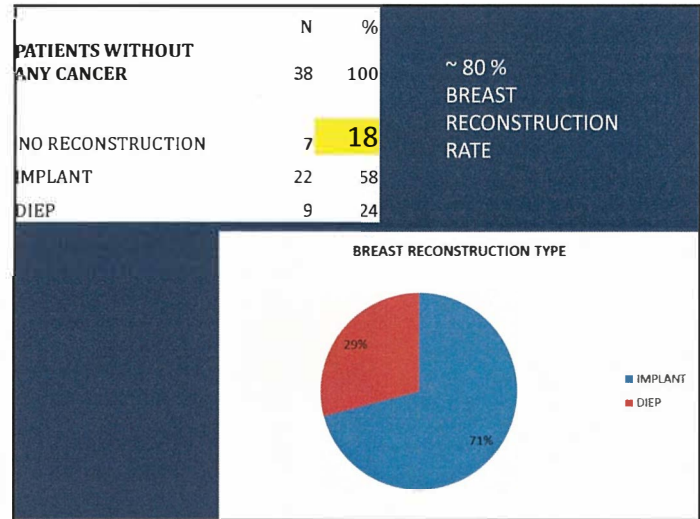
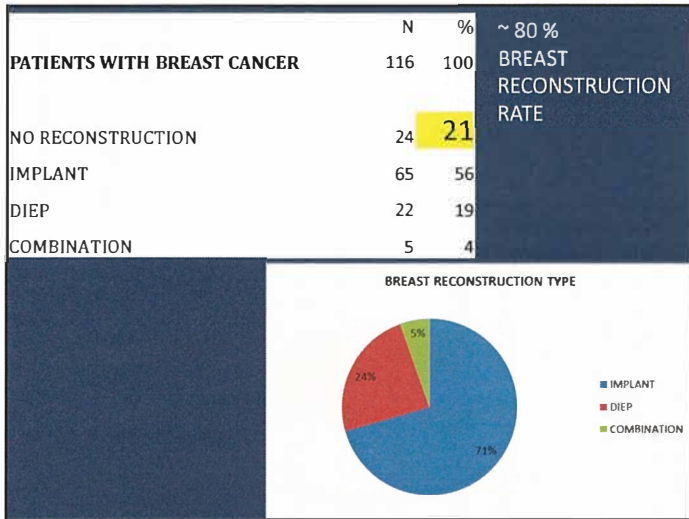
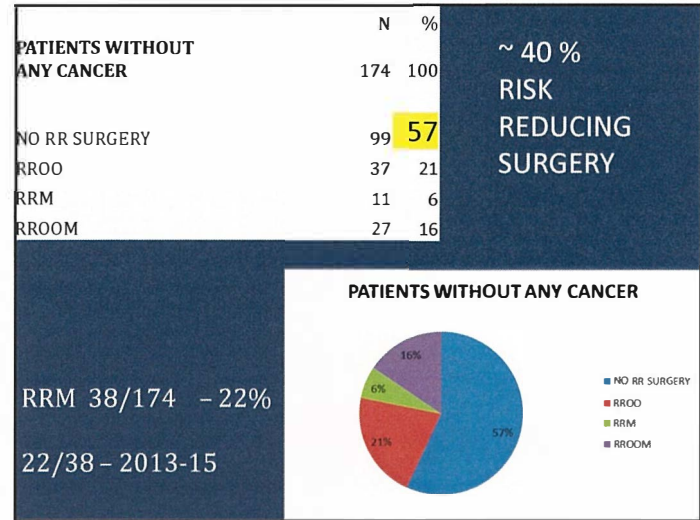
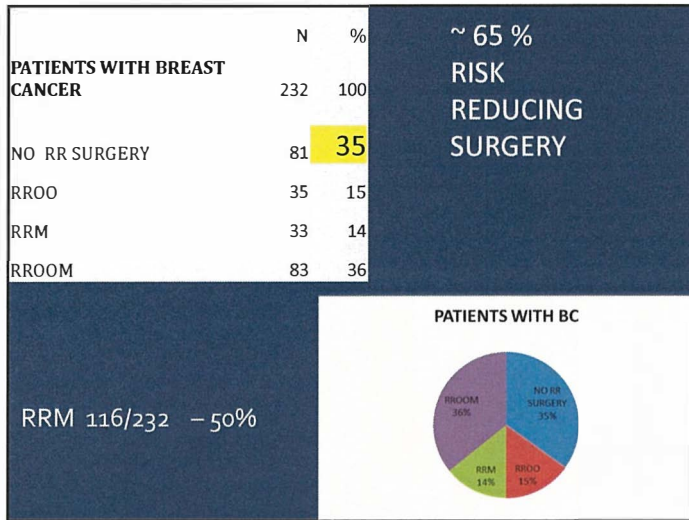
- Evaluate the uptake of the risk reducing surgery in BRCA 1 and BRCA 2 mutation carriers in Slovenia
- Analyze the breast reconstruction rate in patients with risk reducing mastectomy
- Comparison of two periods
 - Until end of 2015
 - Year 2016

PATIENTS INCLUDED until end of 2015

- FEMALE, BRCA 1 AND BRCA 2 MUTATION POSITIVE
- DATA AVAILABLE
- NO CANCER HISTORY (n= 174)
OR
- BREAST CANCER AT ANY TIME (n=232)
- PATIENTS WITH OTHER CANCER TYPES WERE EXCLUDED

PATIENTS INCLUDED until end of 2015

- FEMALE, BRCA 1 AND BRCA 2 MUTATION POSITIVE
- DATA AVAILABLE
- NO CANCER HISTORY (n= 174)
OR
- BREAST CANCER AT ANY TIME (n=232)
- PATIENTS WITH OTHER CANCER TYPES WERE EXCLUDED

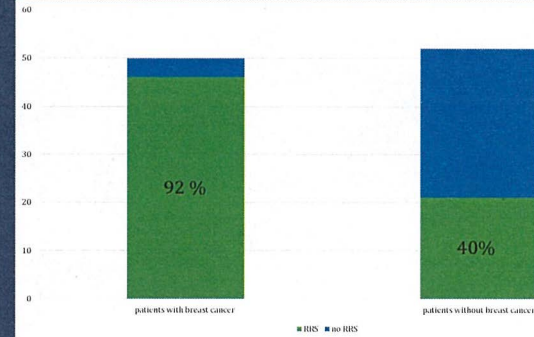


PATIENTS INCLUDED year 2016

- 102 patients
- NO CANCER HISTORY (n= 52)
OR
- BREAST CANCER AT ANY TIME (n=50)
- EXCLUDED 97 carriers
 - 26 male patients
 - 39 ovarian cancer patients
 - 7 Bilateral BC patients
 - 22 missing data!
 - 4 others

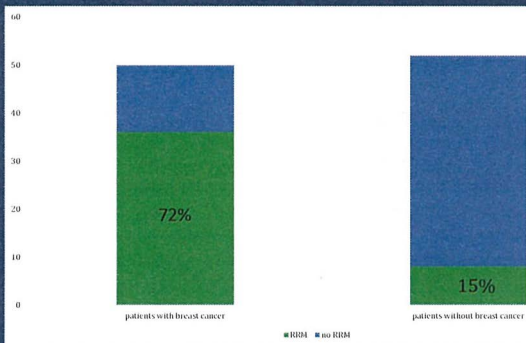
Risk reducing surgery of any type

	patients with breast cancer	patients without breast cancer
RRS	46	21
no RRS	4	31



RRM

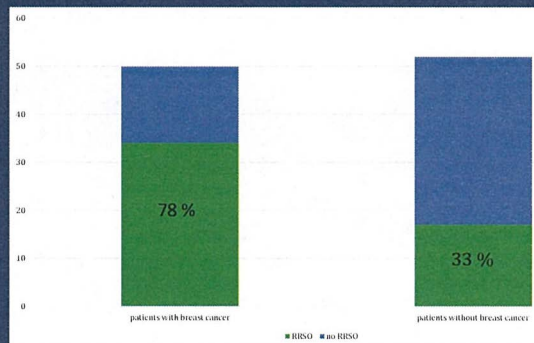
	patients with breast cancer	patients without breast cancer
RRM	36	8
no RRM	14	44



RROO

	patients with breast cancer	patients without breast cancer
RRSO	34	17
no RRSO	16	35

← 22/35 age > 40



Breast Reconstruction rate

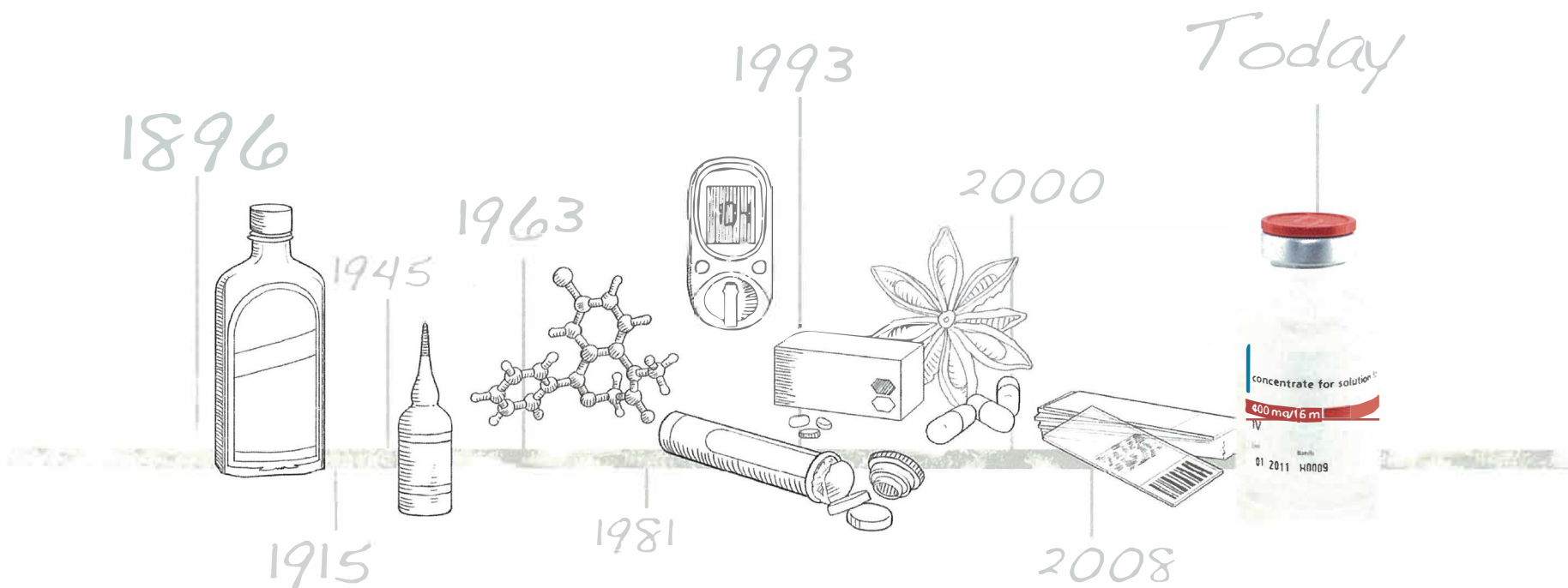
- Patients with BC
– 33/36 92%
- Patients without BC
– 8/52 15%

comparison

		until 2015		2016
any RRS	with BC	65%	with BC	92%
	without BC	40%	without BC	40%
RRM	with BC	50%	with BC	72%
	without BC	22%	without BC	15%
RROO	with BC	51%	with BC	78%
	without BC	37%	without BC	33%

conclusion

- Patients with a history of BC have a higher uptake of risk reducing surgeries compared to patients without cancer
- The overall risk reducing surgery uptake is becoming higher
- Patients at hereditary risk performing PM have a higher rate of immediate breast reconstruction compared to patients with sporadic BC



*Za boljše življenje.
Že vse od 1896.*

Tradicija napredka znanosti in
medicine. Včeraj, danes in jutri.

