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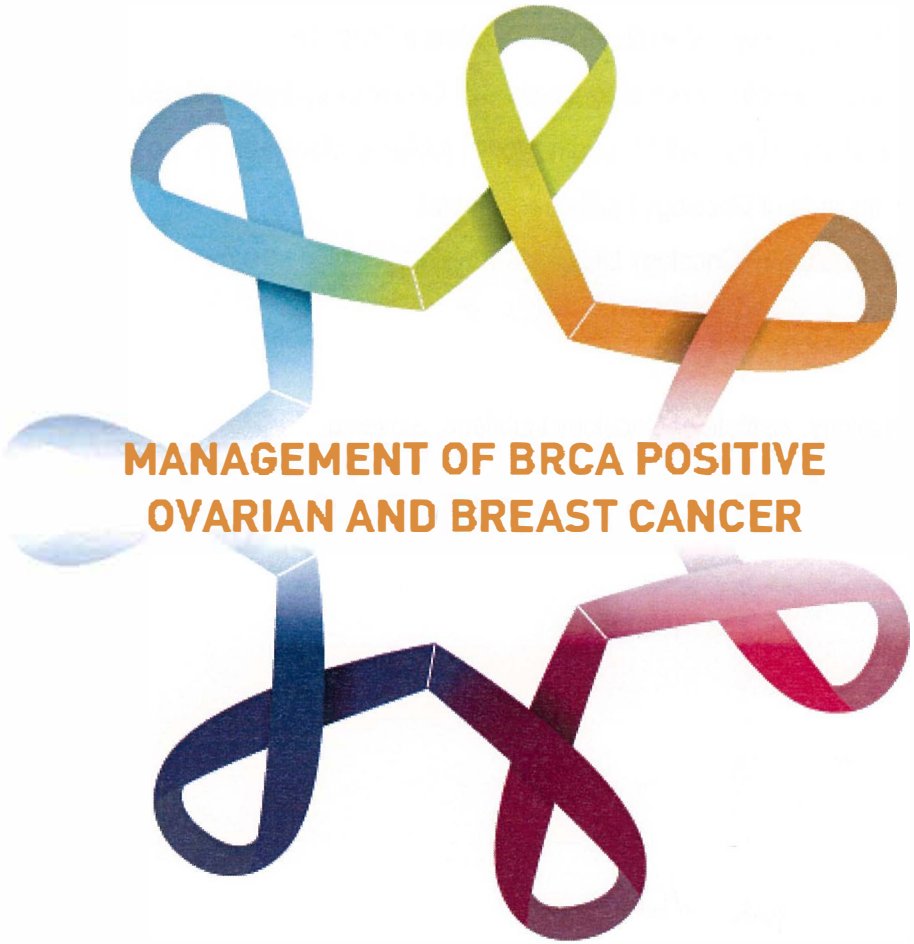

MANAGEMENT OF BRCA POSITIVE OVARIAN AND BREAST CANCER

7.4.2016

Ljubljana, Hotel Union

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ORGANIZERS AND PUBLISHERS:

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Ljubljana, 7. 4. 2016

PROGRAM:

15.30 - 16.00 *Participants gathering*

16.00 - 16.05 Opening and welcome speech, **Mateja Krajc**

16.05 - 16.55 PARP inhibitors in ovarian cancer – a look back and a look forward, **Stan Kaye**

16.55 - 17.45 BRCA1/2 associated breast cancer, **Gareth Evans**

17.45 - 18.00 *Coffee Break*

18.00 - 19.30 Moderated discussion and case presentations:

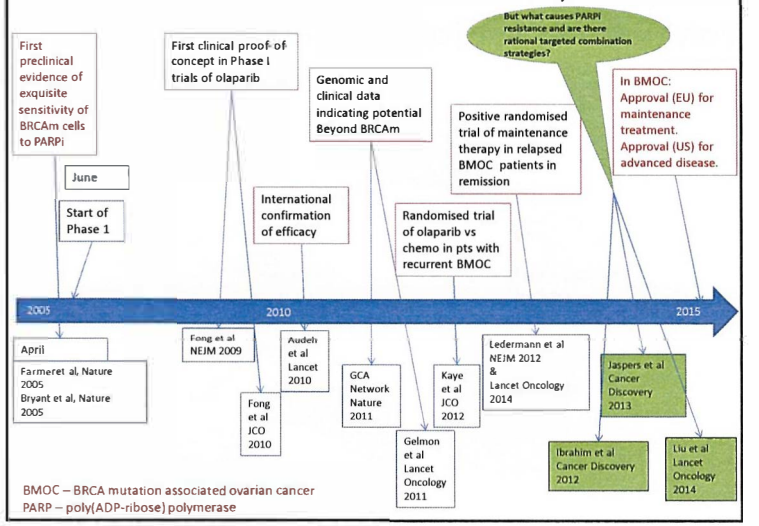
- BRCA genes and genes beyond BRCA – genetic testing from germline to somatic mutations - laboratory experiences, **Srdjan Novaković**
- Cancer genetic counselling and testing - from preventive medicine to treatment, **Mateja Krajc**
- First Slovenian experiences with olaparib in treatment of ovarian cancer, **Erik Škof**
- Surgical treatment of BRCA positive breast cancer patients - 15 years of Slovenian experiences, **Janez Žgajnar**

PARP inhibitors in the treatment of ovarian cancer – lessons from the first 10 years and beyond

Professor Stan Kaye
Royal Marsden Hospital
London

Ljubljana
April 2016

PARP inhibitors for the treatment of ovarian cancer – the first 10 years.



What is homologous recombination?

- Type of genetic recombination in which nucleotide sequences are exchanged between 2 similar /identical strands of DNA – first described 100 years ago.
- Universal biological mechanism, an essential process whereby cells accurately repair potentially harmful double strand breaks in DNA during cell division.
- Decreased rate, i.e. homologous recombination deficiency (HRD) causes inefficient DNA repair and increased susceptibility to cancer
- HRD also provides opportunity to treat cancer by targeting that weakness

Fig. 64. Scheme to illustrate a method of crossing over of the chromosomes.

Morgan T. 1916 , Critique of the theory of evolution

Intracellular proteins involved in homologous recombination deficiency

.....include loss of function of.....

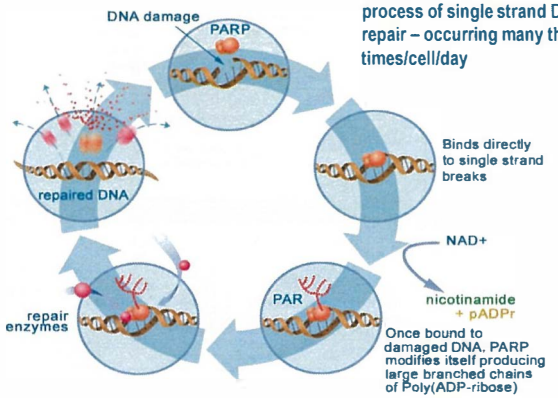
BRCA 1
BRCA 2
RAD 51
RAD 54
DSS 1
RPA 1
NBS 1
ATR
ATM
CHK 1
CHK 2
FAN CD 2
FANC A
FANC C
etc.

Key proteins whose dysfunction is closely linked to ovarian and breast cancer predisposition

Provides opportunity for selective treatment using PARP inhibitors

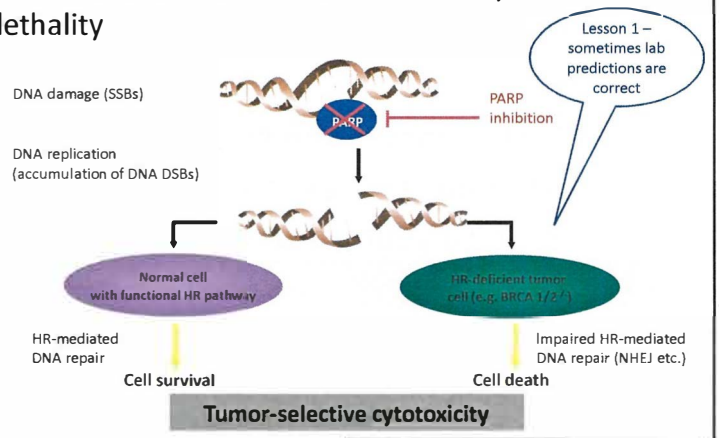
McCabe et al: Cancer Research 66: 8109-8115, 2006

Poly(ADP-Ribose) Polymerase (PARP)



Key enzyme in normal cellular process of single strand DNA repair – occurring many thousand times/cell/day

PARP inhibition and tumor-selective synthetic lethality

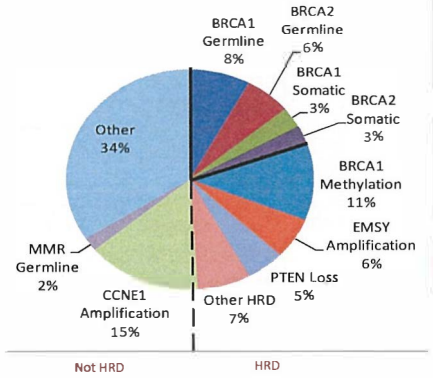


Lesson 1 – sometimes lab predictions are correct

DSB, double-strand break;
HR, homologous recombination
SSB, single-strand break
NHEJ, non-homologous end joining

PS PARP inhibitors can also trap cytotoxic PARP-DNA complexes; clinical relevance unclear.
Murai et al. Canc. Res. 2012 72 5588-5599

The incidence of BRCA mutations in high grade serous ovarian cancer



- BRCA 1/2 germline mutation 14%
- BRCA 1/2 somatic mutation 6%
- Total 20%

BRCA germline mutation testing should be routine…?somatic testing too

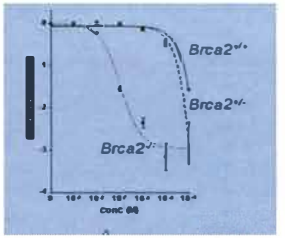
Approx 50% of HGSOC could be candidates for PARPi

The Cancer Genome Research Network – integrated genomic analysis of ovarian carcinoma. Nature 2011 474 609-615

Olaparib, Chapter 1, 2005-9

Pre-clinical → Early clinical trials (Phase I incl. IB)

Exquisite preclinical efficacy of PARPi in BRCA deficient ES cells



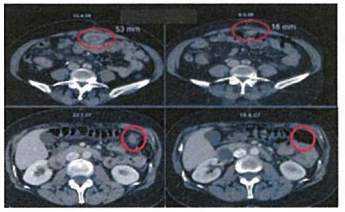
Clonogenic survival curves with inc. concentration of KU 58948

KU-0058948 IC_{50} = 3.4nM

1250 fold difference in SF50 between BRCA2 -/- and +/+

Farmer et al, Nature 434 917-921 2005
also Bryant et al, Nature 434 922-926 2005

Phase I trial of KU59436 (olaparib) indicated excellent tolerance and expansion in 50 BRCA patients showed 46% response.



Fong P et al. N Engl J Med, 2009; 361, 123-134;
Fong P et al. J Clin Oncol, 2010; 28, 2512-2519

"this is nothing like chemotherapy"

Lesson 2 – listen to the patient

Olaparib, a novel, orally active and well tolerated PARP inhibitor

- Olaparib (AZD2281; KU-0059436) 400 mg bd is the maximum tolerated dose[1] with maximum PARP inhibition at 100mg bd, and tumour response at 100–400 mg bd
- **Most common toxicities:** CTCAE grade 1 and 2 nausea and fatigue ; rare toxicity – neuro-cognitive.

46% (23/50 pts) combined response rate (RECIST and CA125) in BMOC[2], in cohort expansion at 200 mg bd, with median response duration of 8 months.

Correlation with platinum-free interval

PFI	< 0	0-6m	>6m
Patient number total 50	13	24	13
Response RECIST and/or CA125 or SD> 4m	3	11	9
percentage	23%	46%	69%

[1] Fong P *et al. N Engl J Med*, 2009; **361**, 123-134;
[2] Fong P *et al. J Clin Oncol*, 2010; **28**, 2512-2519

International Phase II trial of olaparib in BRCAm associated ovarian cancer

57 pts (BRCA 1 39; BRCA 2 18) received either 400 mg bd or 100 mg bd in two sequential cohorts – (med. 3 prior CT) Audeh MW *et al.*, 2010, *Lancet* **376**: 245-51

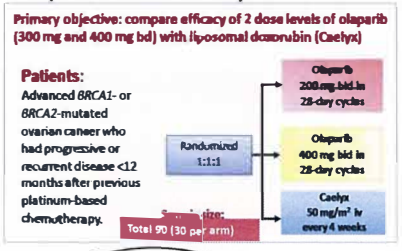
33 pts at 400 mg bd	RECIST response Clinical benefit (incl. CA125 response)	11 (33%) 22 (66%)
24 pts at 100 mg bd	RECIST response Clinical benefit (incl. CA125 response)	3 (13%) 10 (42%)

Conclusion:
- Level of efficacy confirmed, med. response duration 9.5 m
- Favorable toxicity profile confirmed
- 400 mg bd appears to be more active than 100 mg bd

Platinum-status	RECIST
Sensitive	8/19 (42%)
Resistant	6/38 (16%)

Key issues for olaparib in BRCA-mutated ovarian cancer:
- How does efficacy compare with standard therapy, e.g. caelyx?
- What is optimal dose?

What is the optimal dose of olaparib, and how does it compare with caelyx?



- efficacy of olaparib (400 mg bd) was as predicted, with response RECIST/CA125) in 59% and median PFS of 8.8 *m*.
- Olaparib (200mg bd) had 38% RECIST / CA125 response; med PFS 6.5 m
- Caelyx was more effective than anticipated (response 39%; median PFS 7.1 *m*), thus no significant difference in primary end-point
- HR 0.88 p = 0.66

Lesson 3:
Beware assumptions about control arm chemo in BRCA patients

- Clinical development strategy changed:
  - maintenance therapy in BRCAm patients
  - evaluation in sporadic ovarian cancer

Kaye SB et al, J.Clin. Onc. 30 372-379 2012

Olaparib, Chapter 2, 2010-2014 - Randomized trial of maintenance olaparib in platinum-sensitive relapsed ovarian cancer – "Study 19"

Study aim and design

Patients:
- Platinum-sensitive high-grade serous ovarian cancer
- ≥2 previous platinum regimens
- Last chemotherapy was platinum-based to which they had a maintained PR or CR prior to enrolment
- Stable CA-125

Olaparib 400 mg po bid
Randomized 1:1
Placebo po bid
Treatment until disease Progression
Primary end point : PFS

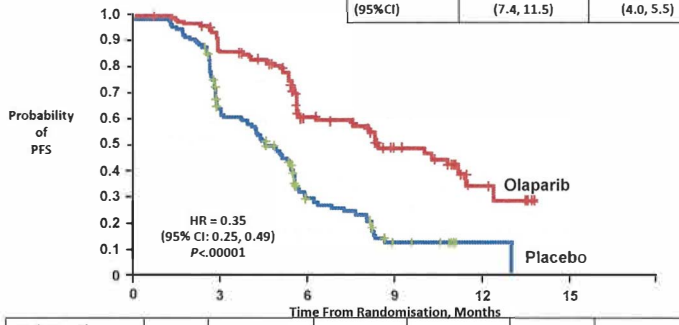
Total of 265 recruited:
- Initially BRCA status known for only 36%
- Subsequent analysis increased this to 96%

Lesson 4:
In PARP inhibitor trials ensure BRCA status can be assessed

Ledermann et al, NEJM 2012 366 1382-192

Study 19: Met PFS Primary Endpoint

	Olaparib N = 136	Placebo N = 129
Median (95%CI)	8.4 mo (7.4, 11.5)	4.8 mo (4.0, 5.5)



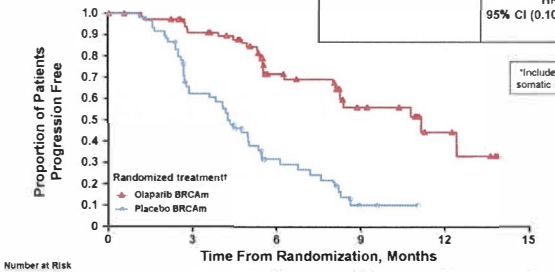
Number at Risk						
Olaparib	136	106	53	24	7	0
Placebo	129	72	24	7	1	0

Ledermann et al, NEJM 2012 366 1382-192

PFS in Patients With a *BRCA* Mutation*

	*BRCA*m (n = 136)	
	Olaparib	Placebo
Events: total patients (%)	26:74 (35.1)	46:62 (74.2)
Median PFS, months	11.2	4.3
	HR = 0.18 95% CI (0.10, 0.31); P<.00001	

*Includes 18 patients with somatic mutations

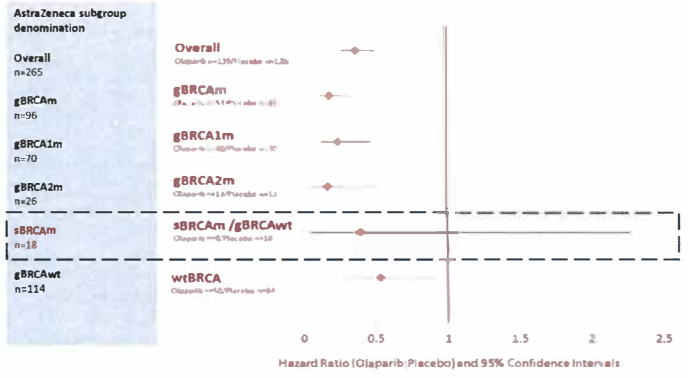


Number at Risk						
Olaparib *BRCAm*	74	59	34	15	5	0
Placebo *BRCAm*	62	35	13	2	0	0

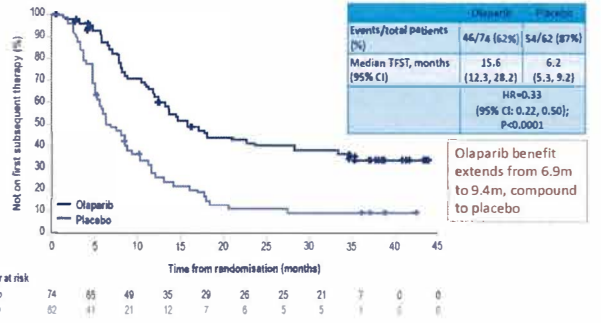
Ledermann J, et al. *Lancet Oncol.* 2014;15(8):852-861.

Analysis of Efficacy in in maintenance study including BRCA WT

Forest Plot of PFS Hazard Ratios by subgroups – FDA analysis (ODAC briefing book)



Study 19: Time to first subsequent therapy (TFST) in patients with BRCAm ovarian cancer

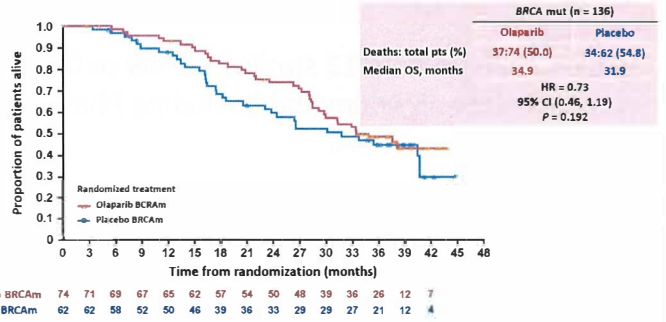


Number at risk										
Olaparib	74	65	49	35	29	26	25	21	7	0	0
Placebo	62	41	21	12	7	6	5	5	1	0	0

Olaparib appears to slow rate of disease growth, even after PD

Ledermann JA, et al. Lancet Oncology 15 852-861, 2014

Overall Survival in Patients With *BRCA* Mutation



- 14/62 (22.6%) placebo patients switched to a PARP inhibitor

Note: only 58% of maturity
-- next analysis – this year ?impact of long-term survivors

Ledermann JA, et al. Lancet Oncology 15 852-861, 2014

Randomized Trial of Olaparib as Maintenance Therapy in Platinum-Sensitive Sporadic Ovarian Cancer

Trial positive for primary endpoint (PFS). But overall survival impact less clear.

Does this reflect cross-over (23%), or too early analysis, or is there an impact of olaparib on subsequent response to chemo, and will this depend on *BRCA* mutation status?

What do we know about PARPi (and platinum) resistance?

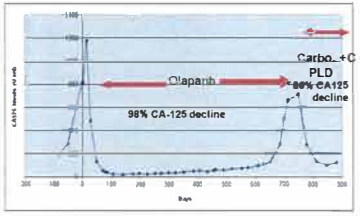
Does PARPi resistance = platinum resistance?

Edwards et al. Nature 2008 451 1111-1115
- Preclinical data in BRCA mutated cells indicate that resistance to both PARPi and platinum can result from secondary mutations in BRCA 1/2 gene, causing reversion to functional BRCA gene, and return of DNA DSB repair capacity.

Barber et al J Path. 2013 229 422-429
- Demonstrate 2 clinical examples of secondary mutations linked to resistance to olaparib.
  - Male patient with BRCAm breast cancer
  - Female patient with BRCAm ovarian cancer

So, is this the answer? When patients become resistant to olaparib, are they resistant to platinum?

Chemosensitivity Post Olaparib in *BRCA*-Mutated Ovarian Cancer



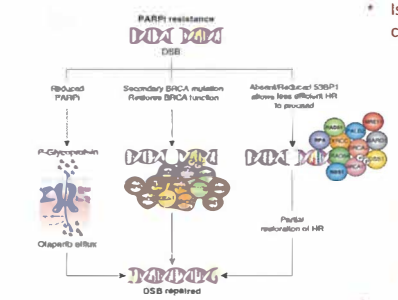
- In 78 evaluable olaparib-treated patients, response to subsequent chemotherapy seen in 36% (24/67) by RECIST and in 45% (35/78) by CA125 and/or RECIST

- For platinum-based treatment:
  - RECIST response in 19/48 (40%)
  - RECIST and/or CA-125 response in 26/53 (50%)
  - Median PFS: 22 weeks
  - Median OS: 45 weeks
- ORR/OS significantly associated with interval since last (pre-olaparib) platinum
- Molecular analysis of tumour resected post-olaparib: No evidence of secondary mutations in 6 cases

What other mechanisms of PARPi resistance may apply?

Ang JE, et al. *Clin Cancer Res.* 2013;19(19):5485-5493.

Resistance to PARP inhibitors



Fojo T, and Bates S, Cancer Discovery 2013 3 20 – 23
Ceccaldi R et al. Canc Res. 2015 75 628
Jaspers et al Cancer Discovery 2013 3 68-81

- Is likely to be multifactorial; factors to consider include:
  - Secondary BRCA mutation
  - P-glycoprotein-based enhanced drug efflux
  - Reduced 53BP1, partially restoring HR
  - NER pathway alterations
- And why do a minority of cases (up to 20%) stay in remission long-term?
- Is this all due to tumour heterogeneity?

Lesson 5 - answers will require tumour samples from patients progressing on PARPi

Long-term responders to olaparib

Pooled analysis from 13 studies – 1489 patients received olaparib 400mg bd (including Phase I/II and maintenance trials).

Of these,
- 137 patients continued for > 2 years
- 84 patients for > 3 years
- 46 patients for > 4 years
- 9 patients for > 5 years
- 4 patients for > 6 years

(including Mrs J.B.)

L'Heureux et al. JCO 32 5S abt 5534, 2014

Mrs J B, aged 59

BRCA 2 mutation positive ovarian cancer

April 2002
- Presented with stage IV disease – pelvic mass, positive pleural effusion
- Surgery then carbo/taxol to August 2002

June 2003 – January 2007
- Four episodes of multi-site peritoneal recurrence
- Treated with carboplatin-based chemo

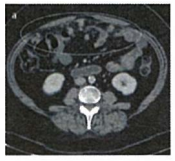
June 2007
- 5th relapse (peritoneal, rising CA125)
- i.e., 5 months after last carboplatin (platinum resistant)
- Began KU59436 (olaparib) in Phase I trial – 200mg bd
- Complete remission and remained in CR until 2014

June 2014
- Isolated liver recurrence, 2cm, segment V

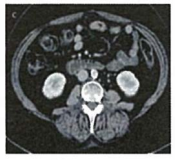
September 2014
- Complete resection, no disease elsewhere
- Continues on olaparib 200mg bd

February 2016
- Progression at 2 sites; for stereotactic RT
- Increase to olaparib 400mg bd

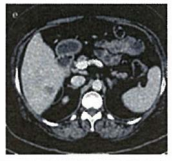
June 2007



Dec 2007



June 2014



Why isn't PARP inhibitor treatment just another form of platinum-based therapy?

- Fundamentally different mechanism of action
- Efficacy in patients with platinum-resistant disease
- Efficacy of platinum in patients progressing on PARP inhibitor.
- Different pace of disease when PARPi resistance develops
- Some very long-term responders

Olaparib in BMOC

- The paths to registration

  a) Maintenance therapy (Europe)

  b) Advanced, recurrent disease (USA)

Olaparib in BRCA mutation associated advanced recurrent ovarian cancer

Kaufman et al, J. Clin Onc 33 244-250, 2015

- non-randomised all-comers (BRCAm) trial of olaparib 400mg bd.
  - n=298, inc. 193 ovarian cancer patients
  - all BMOC patients platinum resistant or "not suitable for further platinum therapy"
  - 77% BRCA1 : 23% BRCA 2
  - RECIST response in 60 (31%)
  - Median PFS = 7.0m; median OS = 16.6m
  - Treatment well tolerated, although 3 patients treated for 6-10m died (2acute leukaemia, 1 MDS)
  - No difference in response between BRCA1 and 2

Overall.....Olaparib in advanced recurrent BRCAm ovarian cancer

Total of 300 patients treated in 6 trials including:

- Initial phase I/II trials
  - Fong et al, NEJM 2009, JCO 2010, Audeh et al Lancet 2010
- Randomised trial vs Caelyx
  - Kaye et al, JCO 2012
- Bioavailability and scheduling studies
  - Capsule » tablet, cont. v intermittent, Mateo et al, EJC 2013
- Non-randomised, multiple BRCAm disease
  - Kaufmann et al JCO 2015

- From the Kaufmann et al paper, data on subgroup of 137 patients who received ≥ 3 lines of chemo presented to FDA for accelerated approval.
  - response rate 34%; response duration 7.9m

Status of olaparib/Lynparza in ovarian cancer – April 2016

a) As capsules (400mg bd)

Europe – approved as **maintenance** treatment for platinum sensitive relapsed BRCA m ovarian cancer – patients in remission following platinum-based therapy.

USA – approved as monotherapy for patients who have received ≥ 3 lines of chemotherapy

- **Not** approved as maintenance therapy
- Approval also for companion diagnostic (Myriad Genetics BRCA analysis CDx)

Status of olaparib in ovarian cancer – April 2016

b) As tablets, 300mg b.d.

- Adaptive 2 stage trial in 196 patients:
  - Confirmed at least bioequivalence for 300mg b.d. tablets cont. compared to 400mg b.d. capsules (Mateo et al, 2016; Targeted Oncology – in press).

- Ongoing randomised trials in ovarian cancer all with 300mg b.d. tablets:
  - SOLO 1 (n=344) – first line, platinum sensitive maintenance vs placebo g BRCAm pts only
  - SOLO 2 (n=264) – second line, platinum sensitive maintenance vs placebo g BRCAm pts only
  - SOLOist (n=157) – second line, platinum sensitive maintenance vs placebo in pts with HRD assoc or somatic BRCA m only.
  - SOLO 3 (n=411) – recurrent platinum sensitive, olaparib vs physician's choice, g BRCAm patients only

PARP inhibitors – what are the next steps?

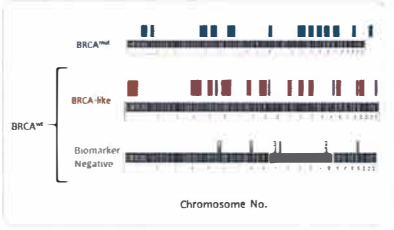
- Define activity in sporadic ovarian cancer and other cancers, e.g. breast, gastric, pancreas, prostate.
- Assess PARP inhibitors other than olaparib (rucaparib, niraparib, BMN-673)
- Develop robust predictive biomarker (including HRD assays)
- Test novel combinations (with P13K or angiogenesis inhibitors, etc.)
- Monitor long-term toxicity
- Understand mechanisms of PARPi resistance

Single agent activity for PARP inhibitors in ovarian cancer

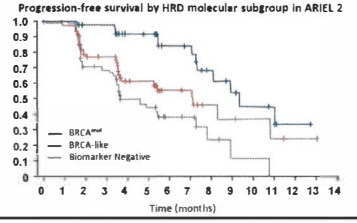
Drug	BRCA Mutation positive			BRCA wild type and unknown			
	n	% resp RECIST	resp. duration	n	% resp RECIST	resp duration	Reference
Olaparib	>100 (most plat resist)	30-60%	7-10m	46	24% (50% in plat sens 4% in plat resist)	7m	Fong et al. JCO 2010 Kaye et al. JCO 2012 Gelmon et al. Lancet Oncology 2011
Rucaparib*	39 (all plat sens)	69%	>9m	74 (HRD high) 62 (HRD low)	30% 13%	7m 4m	McNeish et al ASCO 2015
Niraparib *	20 (9 plat sens)	45%	11m	20	15%	5m	Sandhu et al. Lancet Oncology 2013
BMN 673	28 (22 plat sens)	68%	>6m				Ramanthan et al EJC 2013 suppl 3 LBA 29

* HRD assays based on loss of heterozygosity (LoH) incorporated into ongoing maintenance trials

Homologous recombination deficiency (HRD) assay - Do we have one?



- HRD causes genome wide loss of heterozygosity (LOH), which can be measured by genome profiling using NGS
- Algorithm developed for LOH score (high/low), i.e. BRCA-like signature, with LOH cut off derived from OS data on cohort of 309 platinum-treated patients.



- Correlation with efficacy of rucaparib in Phase II trial – ARIEL 2

BRCA-like :	HRD high	PFS· 7m
Biomarker neg:	HRD low	PFS 4m

McNeish et al. ASCO 2015

Homologous recombination deficiency (HRD) assay - Do we have another?

Haluska P et al, NCI/EORTC/AACR 2014 (EJC 50 supp 6 abst 214 page 72)

Developed HRD score incorporating 3 components:

- Loss of heterozygosity (LOH)
- Telomeric allelic imbalance (TAI)
- Large-scale state transitions (LST)

HRD score is sum of LOH + TAI + LST scores

- Presented evidence of correlation between HRD score and in vitro/in vivo response to niraparib in 106 tumour samples
  - clinical data in ovarian cancer awaited.

Thus:

- Two assays under further evaluation, as key elements in 2 ongoing randomised maintenance trials, with niraparib and rucaparib in sporadic and BRCAm associated ovarian cancer.

Olaparib in other disease types

Studies using 300mg bd tablets:

Breast cancer:
- Olaparib vs placebo in gBRCAm TNBC, post-neoadjuvant CT or adjuvant CT
- Olaparib vs physician's choice in metastatic gBRCAm disease.

Gastric cancer:
- Weekly taxol and olaparib vs weekly taxol and placebo in metastatic disease post first-line chemo.

Pancreatic cancer:
- Maintenance olaparib vs placebo in gBRCAm patients in remission following platinum-based chemo.

Olaparib in other disease types

Prostate cancer

- 49 patients with metastatic endocrine-resistant disease – received 400mg bd tablets
  - 16 (33%) had RECIST/PSA or CTC response, with median treatment duration of 40 weeks

  - Of these 16, a total of 14 had DNA repair defects in tumour samples
    - 7 BRCA 2 (4 somatic, 3 germ-line)
    - 4 ATM mutations
    - 3 other (FANCA/BRCA 1; PALB2; HOAC2)
  - Predictive accuracy of biomarker: 81%

Mateo et al, NEJM 2015 373 16971708

PARP inhibitor – combination strategies

Aim: enhance activity of PARPi by increasing HRD in treated cells

Pre-clinical and early clinical data with:

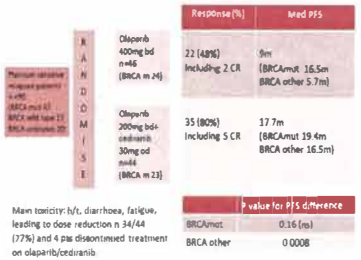
- Antiangiogenic agents[1]
- P13K/AKT pathway inhibitors[2]
- Wee1 Kinase inhibitors[3]
- ATR inhibitors[4]

[1] Chan N & Bristow R. Clin Can Res. 2010 **16** 4553-60
[2] Rehman et al. Cancer Discovery. 2012 **2** 982-84
[3] Karnak D et al. Clin Canc Res 2014 **20** 5085-5096
[4] Huntoon C et al Canc Res 2013 **73** 3683-3691

Antiangiogenic agents/PARP inhibitors

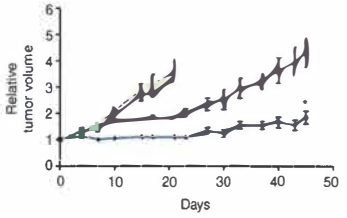
- Complementary targets/mechanisms of action
- Potential enhancement of sensitivity to PARPi by increasing HRD through changes in oxygenation caused by antiangiogenic agent.
- Bevacizumab/olaparib – Phase I trials confirmed feasibility and randomised trial planned.
- Cediranib/olaparib – positive randomised trial presented at ASCO 2014 – further randomised trials (incl. maintenance) ongoing.

Will benefit mainly be in patients with BRCA WT?



Dean et al. BJC 2012 106 468-474
Liu et al. Lancet Oncology 2014 15 1207 1214

PARP inhibitor plus PI3K inhibitor



Control –
BKM 120 –
Olaparib –
BKM plus olaparib –

- preclinical data in TNBC cells demonstrate that P13K inhibition suppresses BRCA 1/2 expression and enhances sensitivity to PARP inhibition, partly through activation of ERK and transcription factor ETS1
- Phase I trials now underway, including olaparib plus AZD5363
  - Initial data encouraging with no overlapping toxicity

Ibrahim et al, Cancer Discovery 2012 2 1036-1047

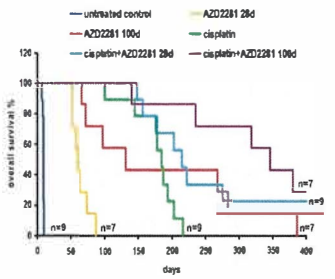
Juvekar et al. Cancer Discovery 2012 2 1036-1047
Rehman et al. Cancer Discovery 2012 2 982-984

PARP inhibitor – combination strategies ? With chemotherapy

Will PARP inhibition enhance efficacy of chemotherapy, e.g. platinum-combination regimes?

Pre-clinical data, including *in vivo* BRCAm model treated with carboplatin and olaparib, confirm potentiation

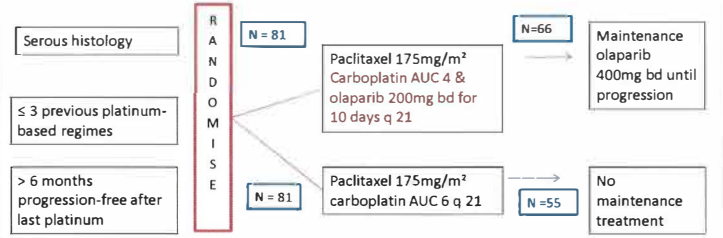
Note: in Phase I clinical trials, enhanced myelosupression noted in first combination schedules, requiring dose reduction both of olaparib and chemotherapy.



Rottenburg et al. PNAS 2008; 105: 17079-17084

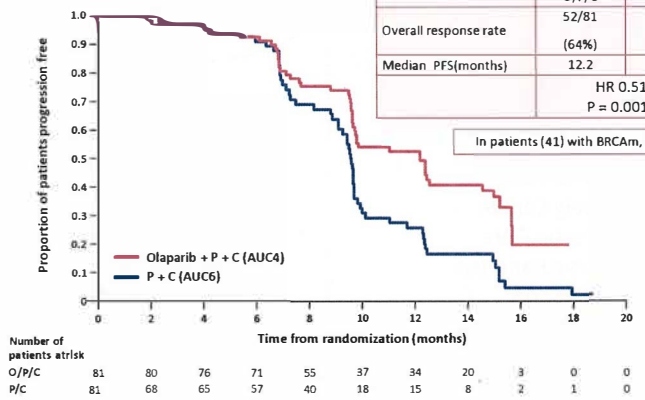
Randomised Phase II study of carboplatin/paclitaxel ± olaparib in platinum-sensitive recurrent ovarian cancer

- **43 sites, 12 countries**
- **162 patients recruited Feb - July 2010**



Oza et al Lancet Oncology 16 87-97 2015

Progression-free survival



	O/P/C	P/C
Overall response rate	52/81 (64%)	47/81 (58%)
Median PFS(months)	12.2	9.6
	HR 0.51 P = 0.0012	

In patients (41) with BRCAm, HR = 0.21

Oza et al, Lancet Oncology 2015

Randomised Phase II study of carboplatin/paclitaxel ± olaparib – Summary and Conclusions

- Overall treatment, including olaparib 400mg bd maintenance, does significantly increase PFS (9.6 – 12.2m, HR 0.51)
- In patients with BRCAm, HR 0.21
- Olaparib has acceptable/manageable toxicity profile

BUT:

- Olaparib 200mg bd (10 days) plus taxol/carbo (AUC 4) does not significantly increase response rate compared to taxol/carbo (AUC 6)
- The PFS benefit can therefore be attributed to maintenance treatment (as in Study 19)
- No evidence of OS benefit (62% maturity)

Emerging questions – the next 10 years of PARP inhibitors in ovarian cancer

a) Should BRCA mutation testing become routine in oncology clinics?
   - If so, should this include somatic (tumour) as well as germ line analysis?
   - But what do we know about tumour heterogeneity?

   Note: germline: somatic mutation frequency is 3-5 : 1

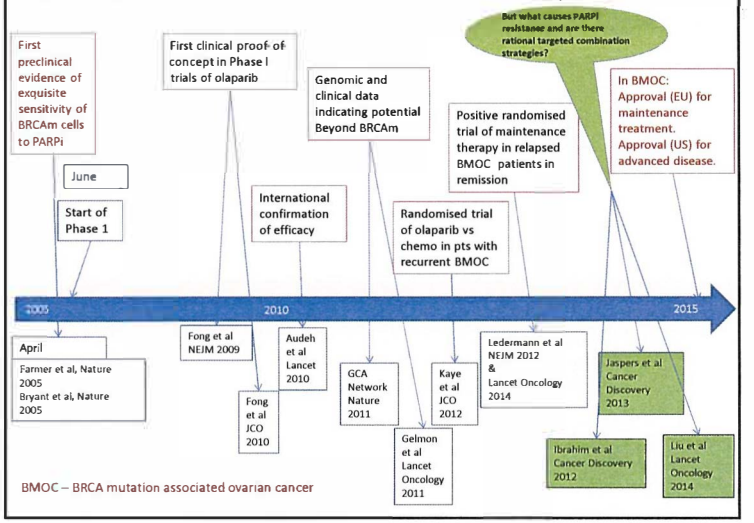
b) Should chemotherapy for BRCAm carriers be the same as or different to BRCA WT patients?
   - Clinical data indicate enhanced efficacy for Caelyx and perhaps Trabectedin as well as platinum

c) How should a BMOC patient with platinum-sensitive relapse be treated?
   - olaparib?
   - bevacizumab?

   Will it vary according to individual patient history?

d) How will PARPi resistance be circumvented
   - novel inhibitors?
   - new combinations, e.g. with WEE-1 or ATR inhibitors?

PARP inhibitors for the treatment of ovarian cancer – the first 10 years.



Summary

The last decade –

- Therapeutic targeting of HRD becomes a reality
- First PARP inhibitor – olaparib – approved for treatment of BRCA mutation-associated ovarian cancer.

The next decade –

- Other applications
- HRD assay
- Combination approaches
- PARPi resistance and its circumvention

Is in safe hands

Acknowledgements

ICR/RMH

- Johann de Bono
- Tim Yap
- Joo Ern Ang
- Peter Fong
- Craig Carden
- Martin Gore
- Susie Banerjee
- Chris Lord
- Alan Ashworth

Lesson 6 – it's the team stupid!

- All the research nurses, clinical fellows and data managers in the DDU
- Support from CRUK, ICR and Biomedical Research Centre at RMH

- Clinical collaborators in Europe, Canada, USA, Australia

Breast cancer in BRCA1/2 carriers

D Gareth R Evans

Christie and St Mary's Hospital Manchester UK

Christie Slovenia Apr 2016

Breast Cancer

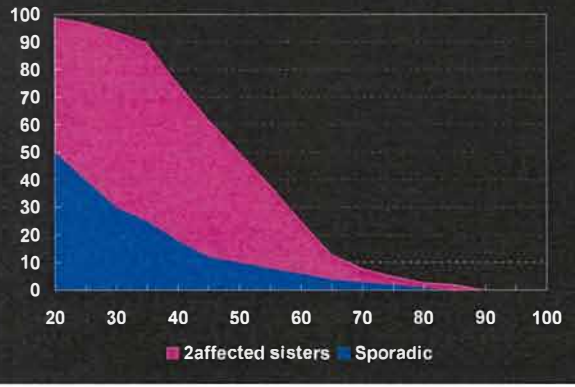
4-5% due to high risk genes (Claus 1994, Newman 1989)

27% have a hereditary element from twin studies (Peto & Mack

Only about 13% of breast cancer accounted for.

Genetic PredIsposition

Importance of age



BRCA1/2 Testing

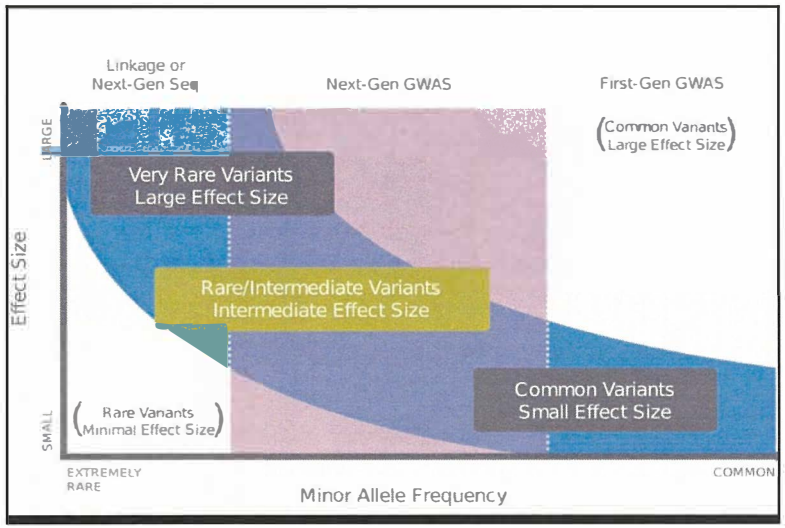
- 2-3% of Breast cancer
- Most families with breast/ovary
- Only a proportion of breast only

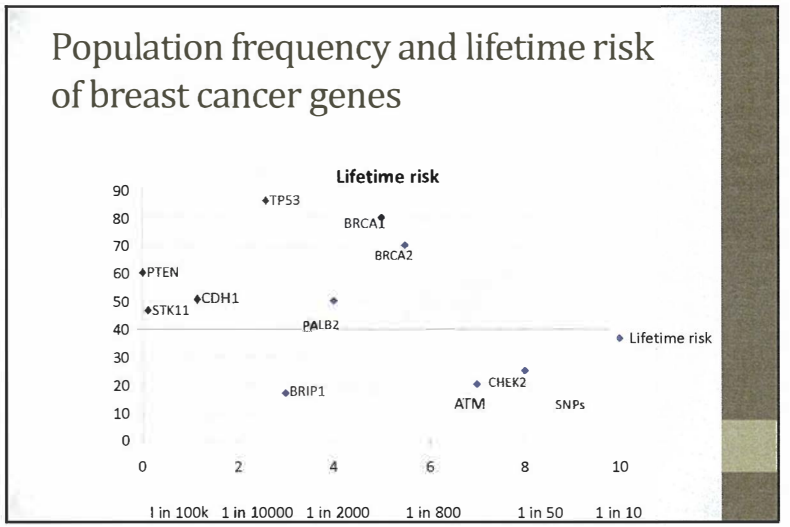
BRCA1/2 testing

4Br/Ov	BRCA1	BRCA2
1 Ov	80%	15%
2 Ov	90%	8%
Male	15%	80%

BRCA1/2 Testing

	BRCA1	BRCA2	BRCAX
4 Br<50	32%	15%	53%
3 Br<50	15%	13%	39%
2 Br<50	8%	7%	35%





Testing for BRCA1/2

- Available since 1996 – technologies changed cost decreased and TAT decreased.
- Originally used for risk prediction, to manage long term risks

BRCA testing since April 2013

- 233 tests on ovarian cancer
- 47 (20.2%) BRCA mutations -36 (15.5%) BRCA1
- 110 sporadic ovarian 10 (9%) with mutation
- 87 high grade serous
- 10/78 (13%) HGS <60 with mutation

BRCA testing since April 2013

- 201 tests on TNT breast cancer
- 44 (22%) BRCA mutations-27 BRCA1
- 80 sporadic TNT 6 (7.5%) with mutation

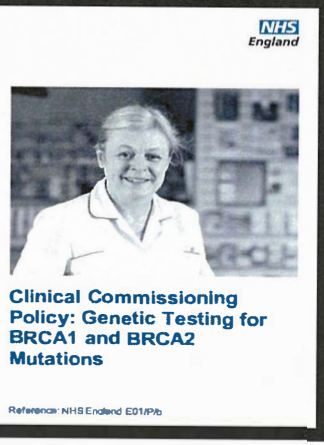
NICE FBC High Risk (tertiary care) Genetic testing

- Offer testing if ≥10% chance of *BRCA1/2* or *TP53* mutation in family
- Start with testing an affected family member
- Must offer full mutation testing-not partial
- By 2005/6 DH target of 8 weeks per gene
- Can now offer to an unaffected individual if no affected relative available

NICE genetic testing affected BC

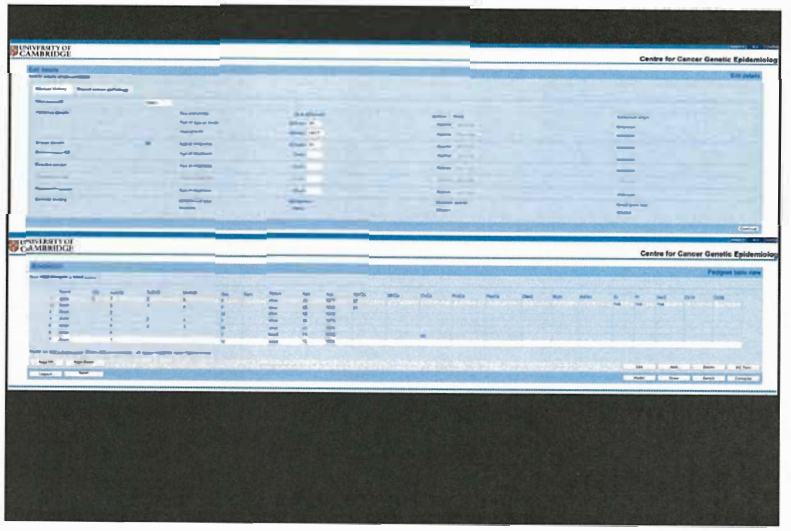
- Offer people eligible for referral to a specialist genetics clinic a choice of accessing genetic testing during initial management or at any time thereafter. **[new 2013]**
- Offer fast-track genetic testing (within 4 weeks of a diagnosis of breast cancer) only as part of a clinical trial. **[new 2013]**
- Discuss the individual needs of the person with the specialist genetics team as part of the multidisciplinary approach to care. **[new 2013]**
- **All requests for fast track testing to be discussed with a consultant in cancer genetics and then, if appropriate, with the laboratory. This will generally only be relevant if a woman is having neoadjuvant chemo (ie chemo before surgery) and the result may help inform treatment decisions**

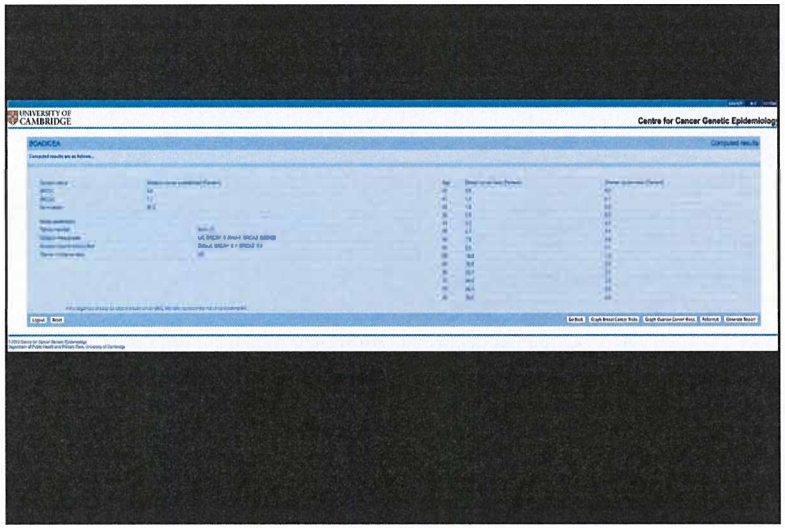
NHS funding at 10% threshold



Scoring systems

- Manual /ballpark-use BCLC data
- Manchester Scoring
- Myriad tables (Frank JCO; 1998, 2002)
- Couch model
- BRCAPRO –Cyrillic
- BOADICEA –only available online





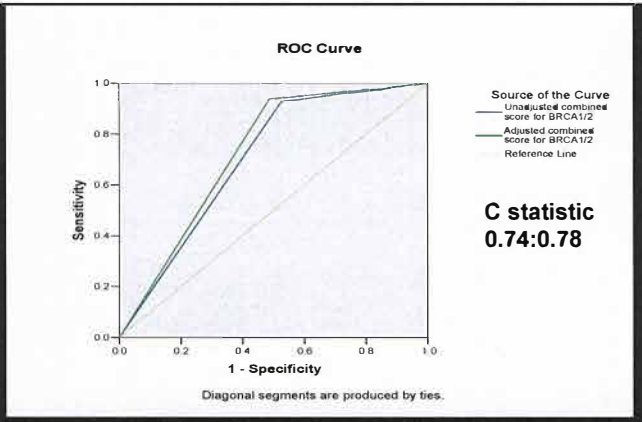
Manchester scoring system

	BRCA1	BRCA2
FBC<30	6	5
FBC 30-39	4	4
FBC 40-49	3	3
FBC 50-59	2	2
FBC>59	1	1
MBC <60	5	8
MBC>59	5	5
Ovarian cancer <60	8	5
Ovarian cancer >59	5	5
Pancreatic cancer	0	1
Prostate cancer <60	0	2
Prostate cancer> 59	0	1

Assessment of score at 20% level

(Evans et al 2005)

Combined score	Numbers	Percentage %
0-9	0/62	0
10-14	10/346	3.5
16-19	37/265	17
20-24	40/195	21
25-29	36/145	28
30-39	56/112	50
40+	51/61	85
Total	230/1200	19



ROC curve with path adjusted score at 20% combined

Pathology adjusted Manchester Score

Pathology	BRCA1 adj	BRCA2 adj
Her2+	-4	0
Lobular	-2	0
DCIS only	-1	0
LCIS only	-4	0
Grade 1 IDC	-2	0
Grade 2 IDC	0	0
Grade 3 IDC	+2	0
ER pos	-1	0
ER neg	+1	0
Grade 3 triple neg	+4	0

Assessment of Manchester score at 10% level (update 2016)

Combined score	Ovarian (%)	Male Breast (%)	All families(%)
40+	99/130 (76)	10/13 (77)	114/156 (73)
40+ (confirmed oc)	73/86 (85)		
35-39	34/62 (55)	8/12 (67)	66/113 (59)
30-34	44/96 (46)	8/13 (62)	88/197 (45)
25-29	74/187 (39.5)	4/20 (20)	124/404 (31)
20-24	76/238 (32)	6/19 (30)	148/639 (23)
15-19	26/197 (13)	3/28 (11)	94/943 (10)
12-14	13/145 (8)	1/11 (9)	31/709 (4.4)
<12	5/90 (5.5)	0/4 (0)	16/674 (2.4)
Total	351/1147 (30.5)	39/121 (32)	681/3835 (18)

Assessment of score at 10% combined score level (TNT)

Combined score	BRCA1 mut	BRCA2 mut	Total (%)
<10	0/3	0/3	0/3 (0)
10-14	7/117	2/117	9/117 (7.6)
15-19	13/110	9/110	22/110 (19)
20-24	26/92	8/92	34/92 (37)
25-29	22/60	8/60	30/60 (50)
30-39	31/45	5/45	36/45 (79)
40 +	20/25	3/25	23/25 (92)
Total	119/451	35/451	154/451 (36)

TNT breast cancer

Study	Country	Age and selection	No tested	BRCA1	BRCA2	Combined BRCA1/2
POSH	UK	< 41 sporadic	43	5 (11.3%)	0	5 (11.6%)
Manchester	UK	<31 unselected	30	11 (37%)	0	11 (37%)
FBCS	UK	< 50 mixture	169	37 (22%)	0	37 (22%)
Gonzalez-Angulo	USA	Unselected	77	11 (14%)	3 (4%)	14 (18%)
Young	Canada	<41 little or no FHx	54	5 (9%)	1(2%)	6 (11%)
Comen	USA	Unselected AJ	64	19 (30%)	6 (95)	25 (39%)

Table 3. Frequency of Mutations by Age at Diagnosis and Family History of Breast or Ovarian Cancer

Family Cancer History	Age at TNBC Diagnosis (years) < 35 Mutation Carriers	< 35 All Patients	< 35 %	35 to 39 Mutation Carriers	35 to 39 All Patients	35 to 39 %	40 to 49 Mutation Carriers	40 to 49 All Patients	40 to 49 %	50 to 59 Mutation Carriers	50 to 59 All Patients	50 to 59 %	≥ 60 Mutation Carriers	≥ 60 All Patients	≥ 60 %
BRCA1															
No breast, no ovarian	14	91	15.4	15	149	10.1	14	209	6.7	13	241	5.4	4	279	1.4
One relative with breast, no ovarian	6	48	12.5	7	50	14	11	103	10.7	3	80	3.8	2	79	2.5
≥ Two relatives with breast, no ovarian	4	12	33.3	5	16	31.3	7	38	18.4	2	28	7.1	1	23	4.3
Any relative with ovarian	3	5	60	6	15	40	6	18	33.3	9	17	52.9	0	7	0
Total	27	156	17.3	33	230	14.3	38	368	10.3	27	366	7.4	7	388	1.8
BRCA2															
No breast, no ovarian	4	91	4.4	8	149	5.4	4	209	1.9	5	241	2.1	2	279	0.7
Any relative with breast, no ovarian	3	60	5	1	66	1.5	4	141	2.8	2	108	1.9	2	102	2
Any relative with ovarian	0	5	0	2	15	13.3	1	18	5.6	1	17	5.9	1	7	14.3
Total	7	156	4.5	11	230	4.8	9	368	2.4	8	366	2.2	5	388	1.3
BRCA1 and *BRCA2*															
No breast, no ovarian	18	91	19.8	23	149	15.4	18	209	8.6	18	241	7.5	6	279	1.4
One relative with breast, no ovarian	7	48	14.6	7	50	14	14	103	13.6	5	80	6.3	4	79	5.1
≥ Two relatives with breast, no ovarian	6	12	50	6	16	37.5	8	38	21	2	28	7.1	1	23	0
Any relative with ovarian	3	5	60	8	15	53.3	7	18	38.9	10	17	58.8	1	7	14.3
Total	34	156	21.8	44	230	19.1	47	368	12.8	36	366	9.8	12	388	3.1
Other genes															
No breast, no ovarian	3	91	3.3	8	149	5	10	209	4.8	7	241	2.9	7	279	2.5
Any relative with breast, no ovarian	2	60	3.3	4	66	6.1	6	141	4.3	6	108	5.6	2	102	2
Any relative with ovarian	0	5	0	0	15	0	0	18	0	1	17	5.9	0	7	0
Total	5	156	3.2	10	230	4.3	16	368	4.3	14	366	3.8	9	388	2.3
All genes															
No breast, no ovarian	21	91	23.1	28	149	18.8	27	209	12.9	25	241	10.4	13	279	4.7
One relative with breast, no ovarian	9	48	18.8	9	50	18	18	103	17.5	8	80	11.3	5	79	6.3
≥ Two relatives with breast, no ovarian	6	12	50	7	16	43.8	10	38	26.3	4	28	14.3	2	23	8.7
Any relative with ovarian	3	5	60	8	15	53.3	7	18	38.9	11	17	64.7	1	7	14.3
Total	39	156	25.0	53	230	23.0	62	368	16.8	48	366	13.4	21	388	5.4

NOTE. Patients with TNBC for whom information was lacking on age at cancer diagnosis or family history of cancer were excluded.
Abbreviation: TNBC, triple-negative breast cancer.

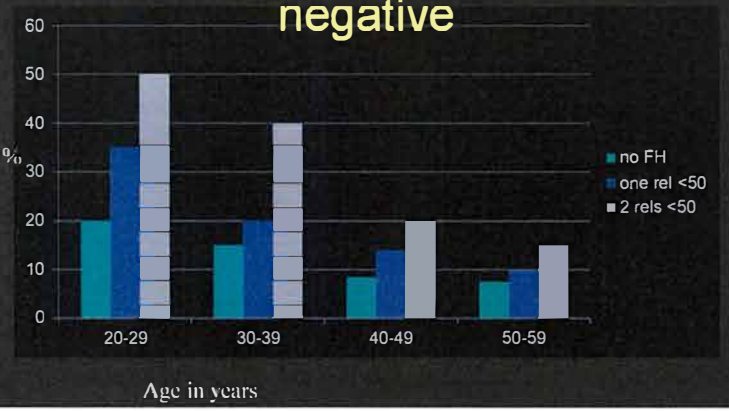
Couch et al J Clin Oncol. 2015;33:304-11.

Table 3. Frequency of Mutations by Age at Diagnosis and Family History of Breast or Ovarian Cancer

Family Cancer History	Age at TNBC Diagnosis (years) < 35 Mutation Carriers	< 35 All Patients	< 35 %	35 to 39 Mutation Carriers	35 to 39 All Patients	35 to 39 %	40 to 49 Mutation Carriers	40 to 49 All Patients	40 to 49 %	50 to 59 Mutation Carriers	50 to 59 All Patients	50 to 59 %	≥ 60 Mutation Carriers	≥ 60 All Patients	≥ 60 %
BRCA1															
No breast, no ovarian	14	91	15.4	15	149	10.1	14	209	6.7	13	241	5.4	4	279	1.4
One relative with breast, no ovarian	6	48	12.5	7	50	14	11	103	10.7	3	80	3.8	2	79	2.5
≥ Two relatives with breast, no ovarian	4	12	33.3	5	16	31.3	7	38	18.4	2	28	7.1	1	23	4.3
Any relative with ovarian	3	5	60	6	15	40	6	18	33.3	9	17	52.9	0	7	0
Total	27	156	17.3	33	230	14.3	38	368	10.3	27	366	7.4	7	388	1.8
BRCA2															
No breast, no ovarian	4	91	4.4	8	149	5.4	4	209	1.9	5	241	2.1	2	279	0.7
Any relative with breast, no ovarian	3	60	5	1	66	1.5	4	141	2.8	2	108	1.9	2	102	2
Any relative with ovarian	0	5	0	2	15	13.3	1	18	5.6	1	17	5.9	1	7	14.3
Total	7	156	4.5	11	230	4.8	9	368	2.4	8	366	2.2	5	388	1.3
BRCA1 and *BRCA2*															
No breast, no ovarian	18	91	19.8	23	149	15.4	18	209	8.6	18	241	7.5	6	279	1.4
One relative with breast, no ovarian	7	48	14.6	7	50	14	14	103	13.6	5	80	6.3	4	79	5.1
≥ Two relatives with breast, no ovarian	6	12	50	6	16	37.5	8	38	21	2	28	7.1	1	23	0
Any relative with ovarian	3	5	60	8	15	53.3	7	18	38.9	10	17	58.8	1	7	14.3
Total	34	156	21.8	44	230	19.1	47	368	12.8	36	366	9.6	12	388	3.1

Couch et al J Clin Oncol. 2015;33:304-11.

Chance of BRCA1/2 in triple negative



Genetic testing for ovarian cancer

- Exclude borderline and mucinous ovarian tumours
- Alsop et al 2012 Journal of clinical oncology
- 1,001 sequentially diagnosed epithelial ovarian cases
- 14% patients had BRCA1/2 germline mutation
  - 22.6% high grade serous
  - 8.4% endometriod
  - 6% in clear cell (but pathology review reclassified 3/4 as high grade serous)
  - 0 in carcinosarcomas
  - diagnosed 61+ with no PSFH. 16/250 (6.4%)-personal comm Mitchell G

What can all be tested at 10%

- TNBC <40 years
- High grade serous Ovarian <61 years

What can be considered for mainstreaming testing for Olympiad (2%) threshold

- All TNT <50 years
- Any TNT with a close rel with OC or MBC
- Aged 50-59 with any family history of BC
- Aged 60-69 with one relative with BC <70
- Aged 70+ with at least one relative aged <50 or two <60

Mutations

- There are potentially 3 results from mutation testing.
- Clearly pathogenic - actionable
- Clearly non-pathogenic – polymorphism – non actionable
- Variant of uncertain significance
  - Evidence may be conflicting, no functional assay, in-silico prediction, segregation studies, tumour studies
  - May move from VUS to either of other catagories
  - c.594-2A>C reclassified from actionable to poly

IARC classification

Proposed Classification System for Sequence Variants Identified by Genetic Testing

Class	Description	Probability of being Pathogenic
5	Definitely Pathogenic	>0.99
4	Likely Pathogenic	0.95–0.99
3	Uncertain	0.05–0.949
2	Likely Not Pathogenic or of Little Clinical Significance	0.001–0.049
1	Not Pathogenic or of No Clinical Significance	<0.001

What risks in VuS

- VuS outside critical regions in BRCA1/2 have <1% chance of being causative
- A VuS should NOT alter risks and decision making

Mainstreaming genetic testing

- Scottish model - genetic testing for ovarian cancer requested by oncologists
- RMH model (MCG)– funded by Wellcome – small centre with large capacity
- GTEOC – collaborative study in Cambridge between oncologists and geneticists
- Liverpool has formal education system for oncologists

Issues around mainstreaming

- Funding of genetic testing
- Time for adequate explanation to patient re:implications – who delivers information – oncologists? Clinical nurse specialists, GC embedded in oncology clinics?
- Timing of testing for patients
- Pathways for returning results – implications for wider family
- Interpretation of results

Impact of genetic diagnosis/testing

psychosocial burden in addition to that of disability and illness

- guilt and responsibility
- adjustment to "at risk" status
- reproductive implications
- risks to extended family

- wish to end uncertainty
- facilitate risk management decisions
- information for children

but

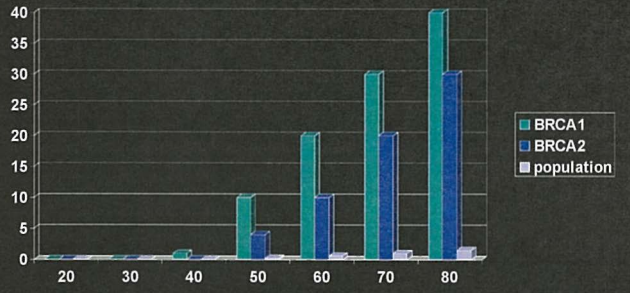
- potential to maintain/increase anxiety about own/other's risk
- limited/radical preventive options
- difficulty disclosing information to relatives
- potential impact on family relationships
- guilt about children's risk

Penetrance estimates

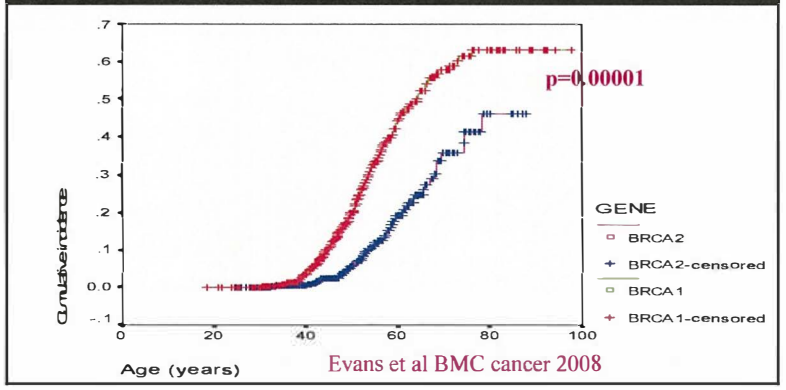
- Vary hugely
- Most studies are retrospective and subject to bias
- Correction for bias may overcorrect for other familial risk
- Population studies provide lower estimates
- BRCA1 BC risks to 70 years 40-87%
- BRCA2 BC risks to 70 years 27-80%

OVARIAN CANCER

Penetrance of susceptibility



Cumulative risks of ovarian cancer in BRCA carriers

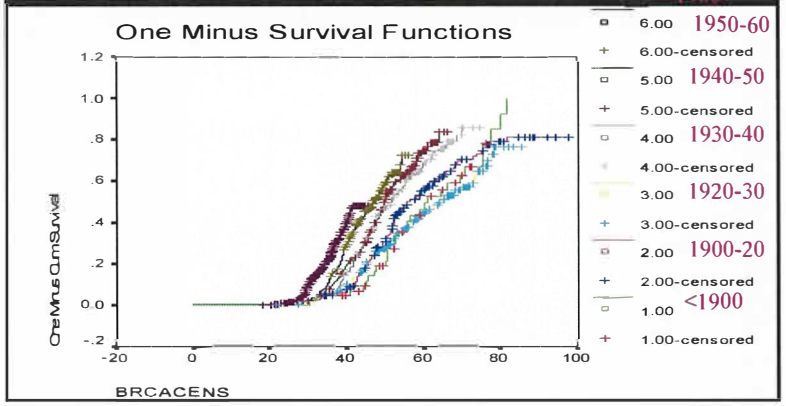


Evans et al BMC cancer 2008

Penetrance for breast and ovarian cancer by age for BRCA1 and BRCA2.

Cancer risk to age	BRCA1 Breast	BRCA2 Breast	BRCA1 Ovary	BRCA2 Ovary
30	3%	4%	0	0
40	21%	21%	3.7%	0
50	44%	51%	21%	4.5%
60	63%	71%	44.5%	18%
70	75% (72-78)	80% (77-83)	61% (58-64)	33% (29-37)
80	85% (82-88)	90% (87-93)	65% (62-68)	38% (34-42)

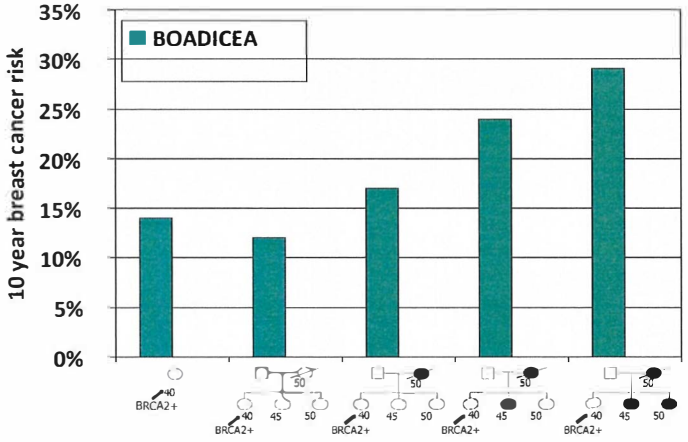
Cumulative risk of breast cancer by age cohort for BRCA1 and BRCA2 combined.



Cumulative risk of breast cancer by age cohort for BRCA1 and BRCA2 combined

Risk to age	King et al <1940	Iceland <1930	UK <1930	King et al 1940+	Iceland >1930	UK 1940+
40	10%		8%	40%		30%
50	23%		30%	65%		55%
60	45%		45%	90%		75%
70	60%	48%	60%		70%	
80	75%		78%			

Genetic Modification of BC Risk in *BRCA1/2* carriers



Methods

- Women only
- Follow up from date of presymptomatic predictive test
- Censor at RRM or death
- Adjust for lead time effect

BRCA1/2 in Manchester

1150 families

- BRCA1 588 kindred
- 58 185 del AG (10%)
- 49 4184 del4 (8%)
- 29 5503C>T (5%)
- 25 546G>T (4%)
- 24 5382 delC (4%)
- 38 dup exon 13 (7%)
- 70 exon deletions (12%)
- 2 other exon dups
- 110 MLPA positive (19%)
- 110/515 (21.4% non AJ)

- BRCA2 562 kindred
- 31 6174 delT (6%)
- 26 2157 delG (4.5%)
- 47 6503 delTT (8.5%)
- 31 MLPA pos (6%)

Presymptomatic tests

Gene	BRCA1	BRCA2
Number	250	238
Median age	36.9	40.8
RRM	81	53
Occult BC at RRM	2	1
BC in follow up	13 (15)	18 (19)
Years follow up	1054.58	1044.46
Rate	14.2 per 1000	18.2 per 1000

Lead time

1st 3 years	486	486	19	1023.16	18.57	11.9 to 29.1		12.59	8.0 to 19.7
2nd 3 years		249	7	571.67	12.24	5.8 to 25.7		12.24	5.8 to 25.7
3rd 3 years		147	5	301.7	16.57	6.9 to 39.8		16.57	6.9 to 39.8

By assuming a lead time of 12 months the rates in the first 3 years was adjusted to 12.6 per 1000 compared to a rate of 13.7 per 1000 for the following 6 years.

COMBINED	Number carriers starting follow up	Number of female carriers contributing	BC	Years follow up	Rates per 1000	95% CI	Cumulative risk to age (%)	Adjusted Rates per 1000	95% CI	Cumulative risk to age adjusted	95% CI
Follow up to 29.99	90	90	2	216.31	9.25	2.3 to 37.0	9.25	6.53	1.6 to 26.1	6.53	
Follow up 30-39.99	186	236	11	616.49	17.84	9.9 to 32.2	27.09	13.71	7.6 to 24.8	20.24	11.3 to 29.2
Follow up 40-49.99	125	205	10	663.09	15.08	8.1 to 28.0	42.17	12.69	6.8 to 23.6	32.93	24.7 to 43.4
Follow up 50-59.99	60	112	7	386.81	18.10	8.6 to 38.0	60.27	15.67	7.5 to 32.9	48.59	42.0 to 61.9
Follow up 60-69.99	21	50	4	188.31	21.24	8.0 to 56.6	**81.51**	19.11	7.2 to 50.9	**67.70**	59.4 to 82.6
Follow up 70-80	4	11	0	27.91	0.00	-	81.51	0.00	-	67.70	
Total	486	704	34	2098.92	16.20	11.6 to 22.7		13.15	9.4 to 18.4		

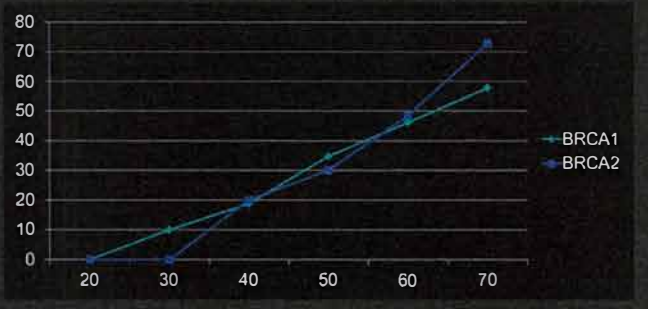
BRCA1	Number carriers starting follow up	Number of female carriers contributing	BC	Years follow up	Rates per 1000	95%	Cumulative risk to age (%)	Adjusted Rates per 1000	95% CI	Cumulative risk to age adjusted	95% CI
Follow up to 29.99 years	56	56	2	141.96	14.09	3.5 to 56.3	14.09	10.10	2.5 to 40.4	10.10	
Follow up 30-39.99	104	132	4	354.56	11.28	4.2 to 30.1	25.37	8.72	3.3 to 23.2	18.83	4.7 to 31.9
Follow up 40-49.99	55	102	6	322.66	18.60	8.4 to 41.4	43.97	15.89	7.1 to 35.4	34.71	20.3 to 48.5
Follow up 50-59.99	26	46	2	150.17	13.32	3.3 to 53.3	57.29	11.35	2.8 to 45.4	46.07	36.0 to 66.8
Follow up 60-69.99	6	17	1	79.51	12.58	1.8 to 89.3	**69.86**	11.69	1.6 to 83.0	**57.76**	46.5 to 79.7
Follow up 70-80	2	4	0	5.72	0.00	-	69.86	0.00	-	57.76	
Total	249	357	15	1054.58	14.22	8.6 to 23.6		11.51	6.9 to 19.1		

BRCA2	Number carriers starting follow up	Number of female carriers contributing	BC	Years follow up	Rates per 1000	95% CI	Cumulative risk to age (%)	Adjusted Rates per 1000	95% CI	Cumulative risk to age adjusted	95% CI
Follow up to 29.99 years	34	34	0	74.35	0.00	-	0.0	0.00		0.00	
Follow up 30-39.99	82	104	7	261.94	26.72	12.7 to 56.1	26.72	20.35	9.7 to 42.7	20.35	15.5 to 25.1
Follow up 40-49.99	70	103	4	340.44	11.75	4.4 to 31.3	38.47	9.75	3.7 to 26.0	30.10	26.7 to 38.3
Follow up 50-59.99	34	66	5	236.74	21.12	8.8 to 50.7	59.59	18.47	7.7 to 44.4	48.57	43.1 to 58.7
Follow up 60-69.99	15	33	3	108.80	27.57	8.9 to 85.5	**72.80**	24.23	7.8 to 75.1	**72.80**	63.7 to 86.7
Follow up 70-80	2	7	0	22.19	0.00	-	**87.17**	0.00	-	**72.80**	
Total	237	347	19	1044.46	18.19	11.6 to 28.5		14.83	9.5 to 23.2		

Familial Factors

- Ten of the prospective breast cancers occurred in families with *BRCA2* Manchester scores of ≥16 out of only 58 pre-symptomatic tests with such a high score. The remaining 10 prospective breast cancer occurred in the remaining 180 patients with lower scores (p=0.01).
- SNP summary scores based on the Turnbull et al weightings for 18 SNPs showed that only 3 breast cancers were in women with SNPs in the lowest tertile (RR <0.715) compared to eight in the intermediate tertile (RR 0.716-1.15) and seven in the highest tertile (RR >1.15). Mean/median scores for breast cancers 1.15/1.05 compared to 1.03/0.88 for those without breast cancer in follow up (p=0.33).

BRCA1/2 penetrance



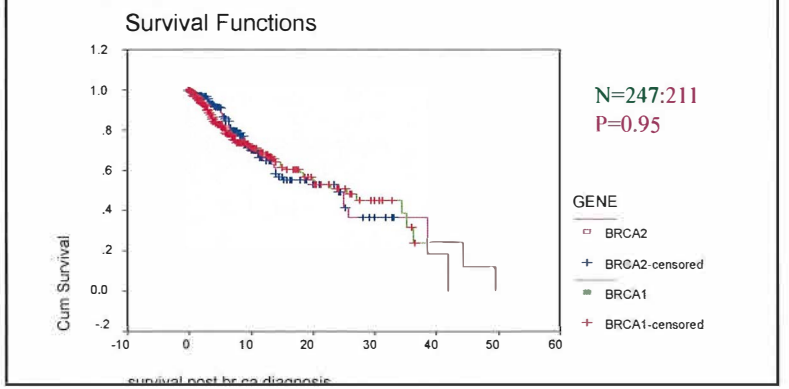
Other prospective studies-EMBRACE

Mavaddat et al JNCI 2013

- Average cumulative risks to 70 years
- BRCA1 -60% (95% CI 44-75%)
- BRCA2 -55% (95% CI = 41-70%)
- BRCA2 carriers in the highest tertile of risk, defined by the joint genotype distribution of 7 SNPs higher risk of developing breast cancer than those in the lowest tertile

HR= 4.1, 95% CI = 1.2 -14.5; P = .02.

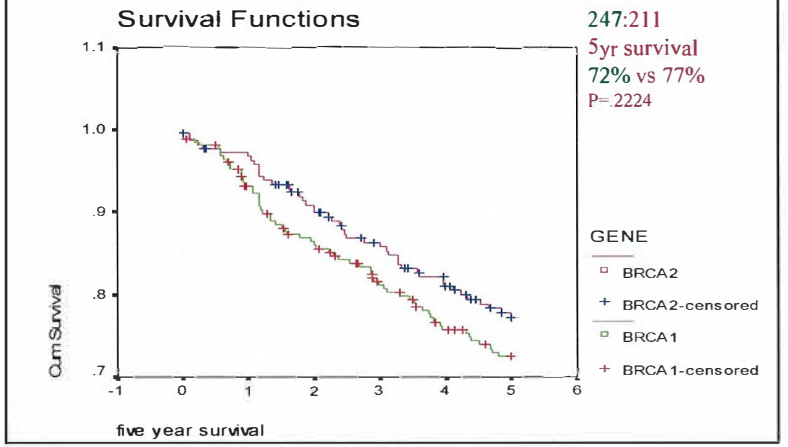
Survival from diagnosis –BC proven carriers and FDRs



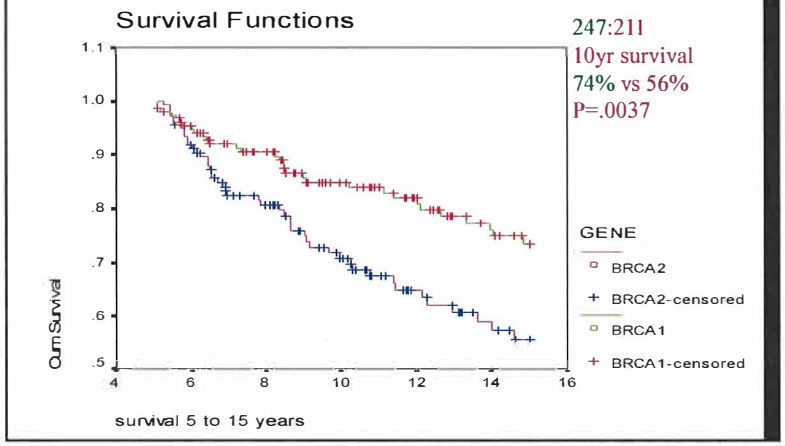
Conclusions

- Women should be given a range of BC risks perhaps
- 45-90% for *BRCA1* and
- 30-90% for *BRCA2*.
- This range reflects the modifying effects of other genetic factors as well as hormonal and reproductive factors. As such clinicians seeing women from high-risk breast cancer families should give women a higher estimate within this range
- In future SNP testing may guide better within the range

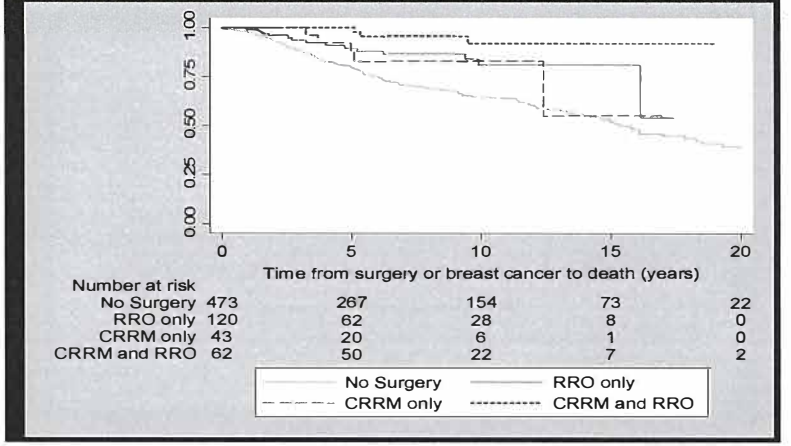
Survival from diagnosis (1980+)-BC



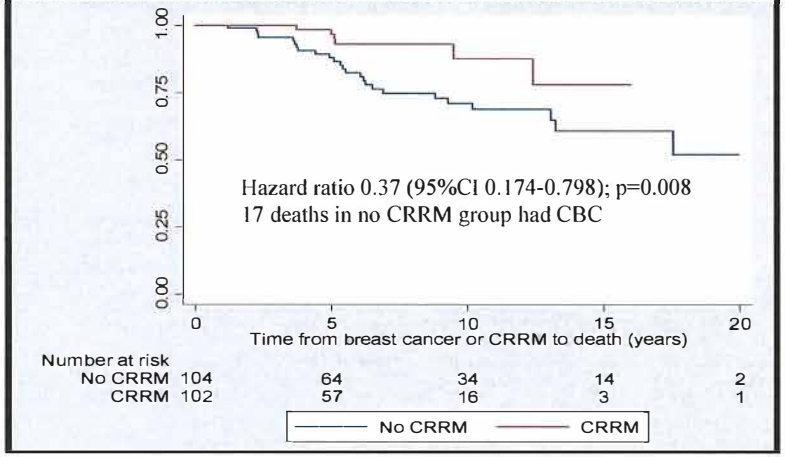
Survival from 5yrs post diagnosis -BC



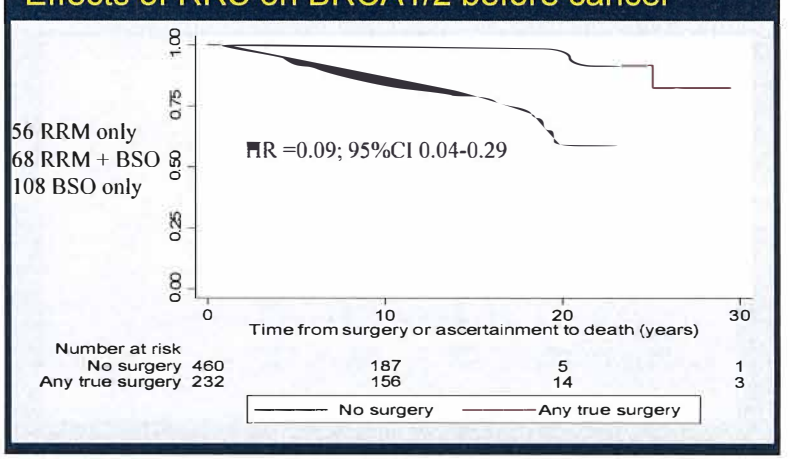
Effect of contralateral RRM Ingham et al BCRT 2013



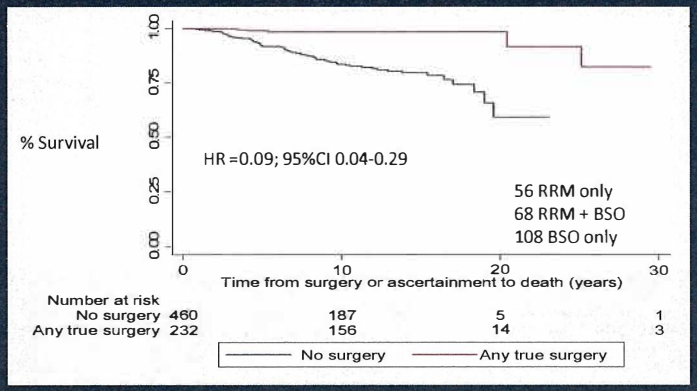
Effect of contralateral RRM 105 cases and controls



Effects of RRS on BRCA1/2 before cancer

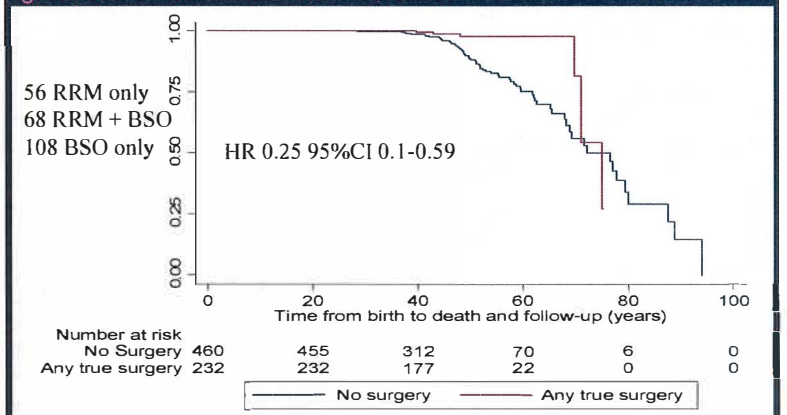


BRCA1/2 carriers – risk reducing surgery



Effects of RRS on BRCA1/2 before cancer

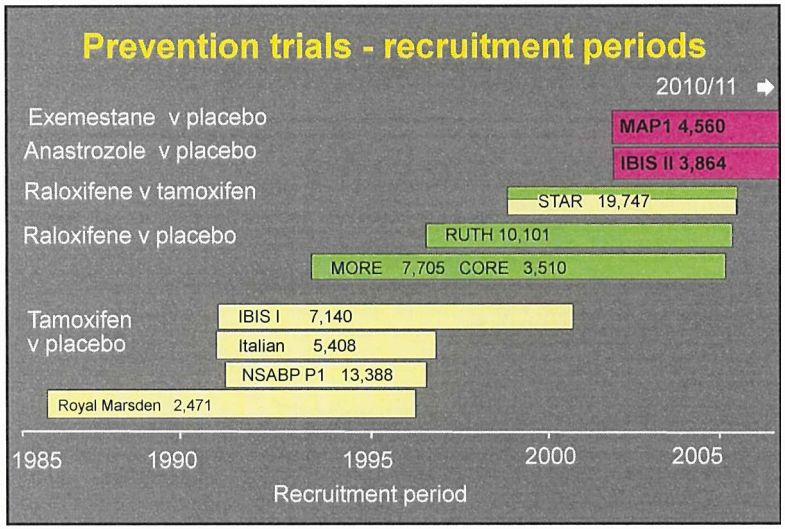
ngham et al Breast Cancer Res Treat 2013



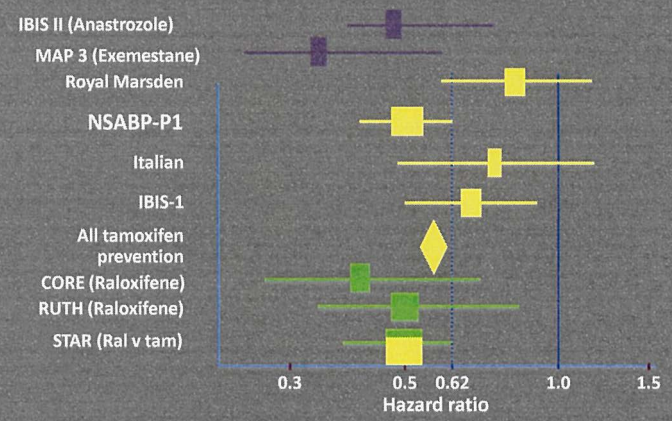
BRCA1/2 carriers - risk reducing surgery

Chemoprevention

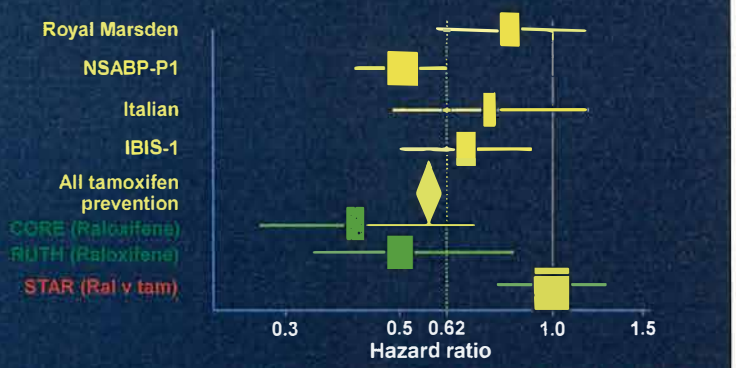
Prevention trials - recruitment periods



Disease Prevention: SERMs & Aromatase Inhibitors



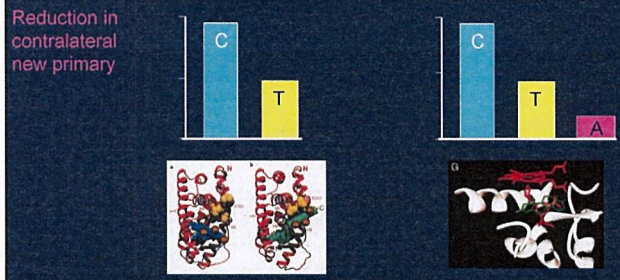
Trial results at about the end of the treatment period



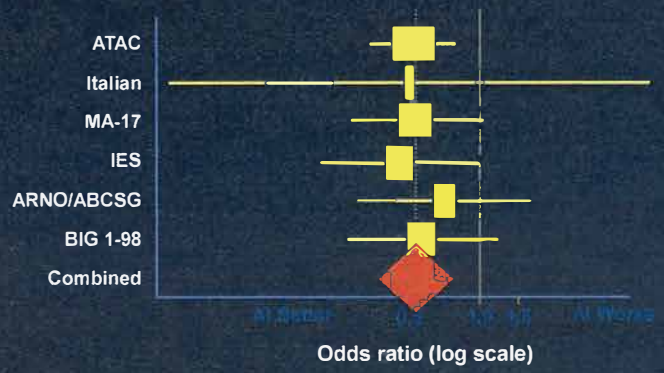
Aromatase inhibitors better than tamoxifen – contralateral breast

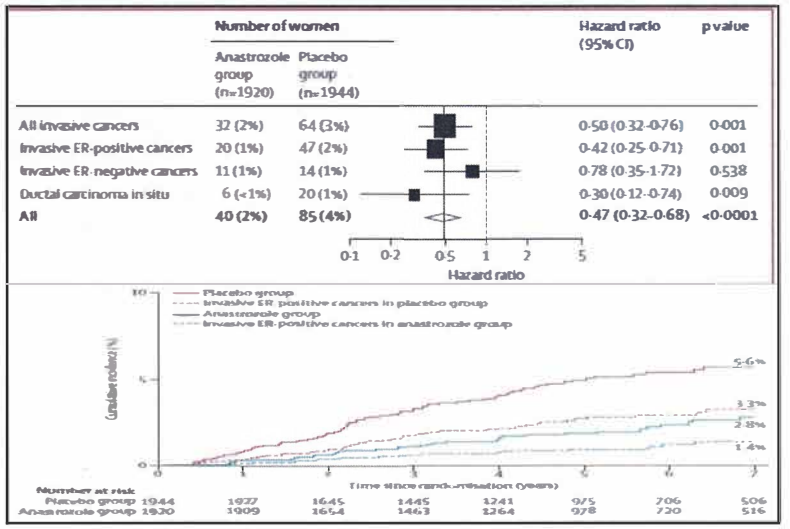
Adjuvant tamoxifen v placebo

Adjuvant tamoxifen v AI



Contralateral Breast Cancers in Aromatase Inhibitor Adjuvant Trials





Future potential agents

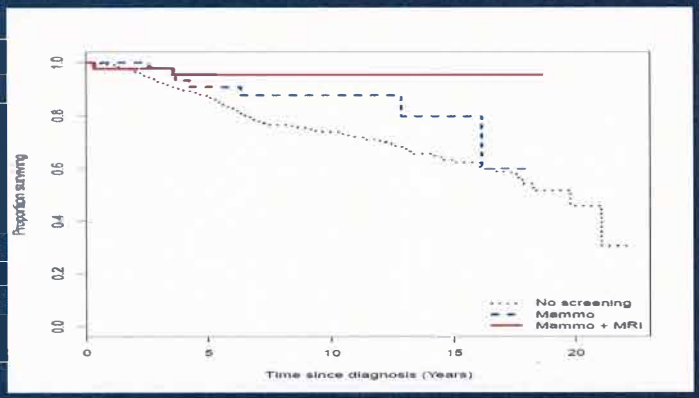
- Antoprogestins (Howell S PI CR003 BCN)
- Denosumab (anti Rank-L)
- Metformin
- PARPi for BRCA

Survival in MRI screened BRCA1/2

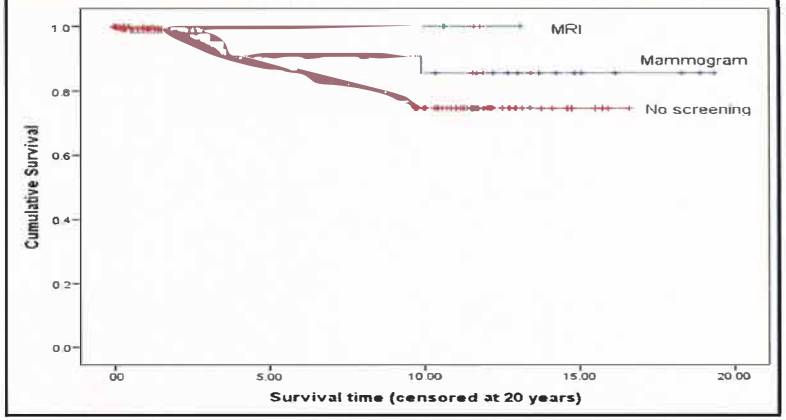
Cohort	Treatment	Follow-up	Number at risk	Number of events	% Overall survival (95% CI)
G1	No screening	5-year	320	59	86.7 (83.6 - 90.0)
		10-year	172	101	73.7 (69.3 - 78.4)
G2	Mammogram	5-year	35	4	90.7 (82.4 - 99.8)
		10-year	18	5	87.7 (78.0 - 98.5)
G3	Mammogram + MRI	5-year	35	2	95.3 (89.3 - 100.0)
		10-year	23	2	95.3 (89.3 - 100.0)

Evans et al Breast Cancer Res Treat 2014

Survival in MRI screened BRCA1/2



MRI Screening in BRCA2 carriers (UK-Norwegian)



Nice: Key Screening Recommendations 2013

Surveillance of people with a personal history and a family history of breast cancer.

- Offer annual MRI surveillance to all women aged 30–49 years with a personal history of breast cancer who are at high risk of contralateral breast cancer or have a BRCA1 or BRCA2 mutation. [new 2013].
- Offer annual mammographic surveillance to all women aged 50–69 years with a personal history of breast cancer who are at high risk of contralateral breast cancer or have a BRCA1 or BRCA2 mutation. [new 2013].

Conclusions 1

- MRI screening is justified aged 30-50-60 in BRCA/TP53 carriers and 50% risk
- Tamoxifen likely to reduce risk by 30-40% even in *BRCA1*
- *Aromatase inhibitors by 50%*
- *Oophorectomy reduces risk by 50%*
- *RRM reduces risk by 90-95%*
- *Both in BRCA normalises life expectancy*

Conclusions 2

- Prevention strategies should reverse the trend of increasing BC diagnosis and fewer BC deaths
- Preventing deaths will be made up of many little victories using many different approaches
- *Early detection is still key as this will allow more cures*

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- Genetic register
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Department of Molecular diagnostics

BRCA genes and genes beyond BRCA – genetic testing from germline to somatic mutations - laboratory experiences

Srdjan Novaković

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CANCER FAMILY SYNDROMES ASSOCIATED WITH HBOC

- BRCA related breast/ovarian cancer syndrome
- Li-Fraumeni (*p53*),
- Cowden (*PTEN*),
- Muir-Torre (*MSH2, MLH1*),
- Peutz-Jeghers (*STK11*),
- Ataxia –teleangiectasia (*ATM*)

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INDICATIONS FOR CLINICAL TESTING

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
BRCA-Related Breast and/or Ovarian Cancer Syndrome

BRCA1/2 TESTING CRITERIA[a,b]

- Individual from a family with a known deleterious *BRCA1/BRCA2* gene mutation
- Personal history of breast cancer[b] + one or more of the following:
  - Diagnosed ≤45 y
  - Diagnosed ≤50 y with:
    - An additional breast cancer primary[c]
    - ≥1 close blood relative[d] with breast cancer at any age
    - ≥1 close relative with pancreatic cancer
    - ≥1 relative with prostate cancer (Gleason score ≥7)
    - An unknown or limited family history[e]
  - Diagnosed ≤60 y with a:
    - Triple negative breast cancer
  - Diagnosed at any age with:
    - ≥1 close blood relative[d] with breast cancer diagnosed ≤50 y
    - ≥2 close blood relatives[d] with breast cancer at any age
    - ≥1 close blood relative[d] with ovarian[e] carcinoma
    - ≥2 close blood relatives[d] with pancreatic cancer and/or prostate cancer (Gleason score ≥7) at any age
    - A close male blood relative[d] with breast cancer
    - For an individual of ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish) no additional family history may be required[f]
- Personal history of ovarian[e] carcinoma
- Personal history of male breast cancer
- Personal history of prostate cancer (Gleason score ≥7) at any age with ≥1 close blood relative[d] with breast cancer ≤50 y or two relatives with breast, pancreatic or prostate cancer (Gleason score ≥7) at any age
- Personal history of pancreatic cancer at any age with ≥1 close blood relative[d] with breast cancer ≤50 y or two relatives with breast, pancreatic cancer or prostate cancer (Gleason score ≥7) at any age
- Personal history of pancreatic cancer and Ashkenazi Jewish ancestry
- Family history only (significant limitations of interpreting test results for an unaffected individual should be discussed):
  - First- or second-degree blood[d] relative meeting any of the above criteria
  - Third-degree blood[d] relative who has breast cancer[b] and/or ovarian[e] carcinoma and who has ≥2 close blood relatives[d] with breast cancer (at least one with breast cancer ≤50 y) and/or ovarian[e] carcinoma

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MUTATION SCREENING

- PCR (polymerase chain reaction)
- HRM (high resolution melting)
- DGGE (denaturing gradient gel electrophoresis)
- DS (direct sequencing)
- NGS (next generation sequencing)
- MLPA (multiplex ligation-dependent probe amplification)

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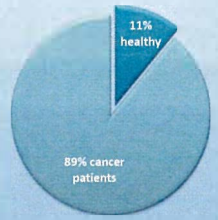
RESULTS OF *BRCA1/2* MUTATION SCREENING 1999 - DECEMBER 2015

- 2325 tested individuals from 1567 Slovene breast and/or ovarian cancer families



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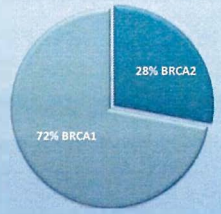
RESULTS OF *BRCA1/2* MUTATION SCREENING 1999 - DECEMBER 2015

- 355 *BRCA1/2* positive families
  - *BRCA1* – 254
  - *BRCA2* – 101



- Mutation detection rate: 22.6% (355/1567)

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BRCA1/2 MUTATION DISTRIBUTION FREQUENCY

All together 355 BRCA1/2 positive families

	NO. OF MUTATIONS	NO. OF FAMILIES	OVERALL RELATIVE APPERANCE FREQUENCY(%)
IN 1 FAMILY ONLY	47	47	13,24
IN 2-10 FAMILIES	24	90	25,35
IN 11-20 FAMILIES	4	59	16,62
IN >20 FAMILIES	4	159	44,79

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BRCA1 AND *BRCA2* SCREENING STRATEGY 1999-2015

Unkown mutation in the family

1. Testing for the most common mutations in Slovene population
2. MLPA-detection of large rearrangements
3. Screening for small deletions and point mutations using:
   - DGGE
   - HRM

   Direct sequencing

The report is informative when a mutation is proven.

The report is noninformative if the mutation is not detected.

Known mutation in the family

Testing for the known mutation

We issue a report with an exact answer: whether the specific mutation is present in the patient blood sample or not.

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Department of Molecular diagnostics

BRCA1 AND *BRCA2* SCREENING STRATEGY

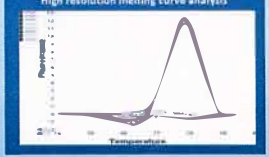
Unkown mutation in the family

Screening with DGGE, HRM and sequencing

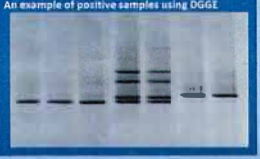
Direct sequencing of fragments positive with DGGE and HRM

Direct sequencing of frequently polymorphic fragments

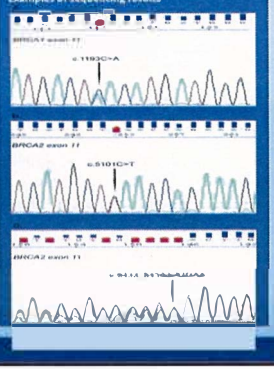
High resolution melting curve analysis



An example of positive samples using DGGE



Examples of sequencing results



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BRCA1 AND *BRCA2* SCREENING STRATEGY 2015-

Unkown mutation in the family

1. MLPA-detection of large rearrangements
2. NGS sequencing
3. Direct sequencing

The report is informative when a mutation is proven.

The report is noninformative if the mutation is not detected.

Known mutation in the family

Testing for the known mutation

We issue a report with an exact answer: whether the specific mutation is present in the patient blood sample or not.

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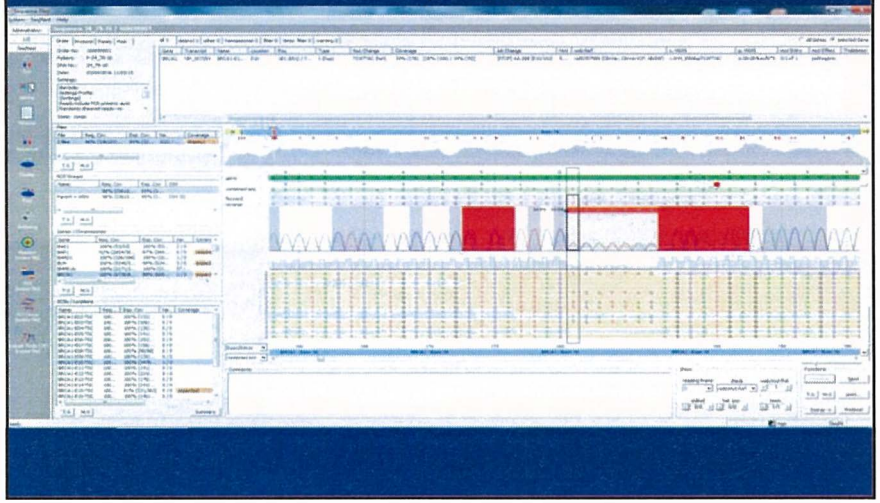

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BRCA 1/2 MUTATION SPECTRUM 1999 - DECEMBER 2015

79 different deleterious mutations:

37 in *BRCA1*
- missense mutations affecting the 5'RING domain
- nonsense mutations
- frame-shift mutations
- deletions of whole exons
- splice site mutations

42 in *BRCA2*
- splice site mutations
- nonsense mutations
- frame-shift mutations

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BRCA 1/2 MUTATION SPECTRUM 1999 - DECEMBER 2015

- The most common mutation found in the *BRCA1* gene was c.181T > G (p.Cys61Gly). It was detected in 66 families.
- The most common mutation in the *BRCA2* gene is a splice site mutation c.7806-2A > G. It was detected in 24 families.

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THE MOST COMMON BRCA1/2 MUTATIONS IN BREAST OR OVARIAN CANCER PATIENTS

DIAGNOSIS	2 the most common mutations
Breast cancer	BRCA1:c.181T>G (p.Cys61Gly), BRCA1:c.1687C>T (p.Gln563*),
Breast + ovarian cancer	BRCA1:c.181T>G (p.Cys61Gly), BRCA1:c.1687C>T (p.Gln563*),
Ovarian + endometrial cancer	BRCA1:c.181T>G (p.Cys61Gly), BRCA1:c.1687C>T (p.Gln563*),

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NGS - GENES TESTED IN BREAST AND OVARIAN CANCER PATIENTS IN 2015

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

Number of patients with different mutations detected in 2015

BRCA1	*BRCA 2*	*TP53*	*STK11*	*PTEN*	*CDH1*	*MSH2*	*MLH1*	*MSH6*	*PMS2*	*EPCAM*	*CHEK2*	*PALB2*	*ATM*
52	23*	1	0	0	3	1	0	0	0	0	5	4	3*

* in a single patient the mutation in *BRCA2* and in *ATM* was detected at the same time

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BRCA1/2 MUTATIONS IN OVARIAN CANCER PATIENTS IN PERIOD 2012-2015

Most ovarian cancer patients have been tested for germline *BRCA* mutations.
Only lately do we provide testing of somatic *BRCA* mutations.

All together 172 tested ovarian cancer patients

GENE	No. of patients with mutation	%	No. Of different mutations
BRCA1	47	78,33%	21
BRCA2	13	21,66%	10
BRCA1/2	60	100%	31

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ONCLUSION:

Genetic testing of *BRCA* genes provides the key to:

- Accurate cancer risk assessment
- Effective genetic counseling
- Appropriate medical follow-up
- Appropriate treatment

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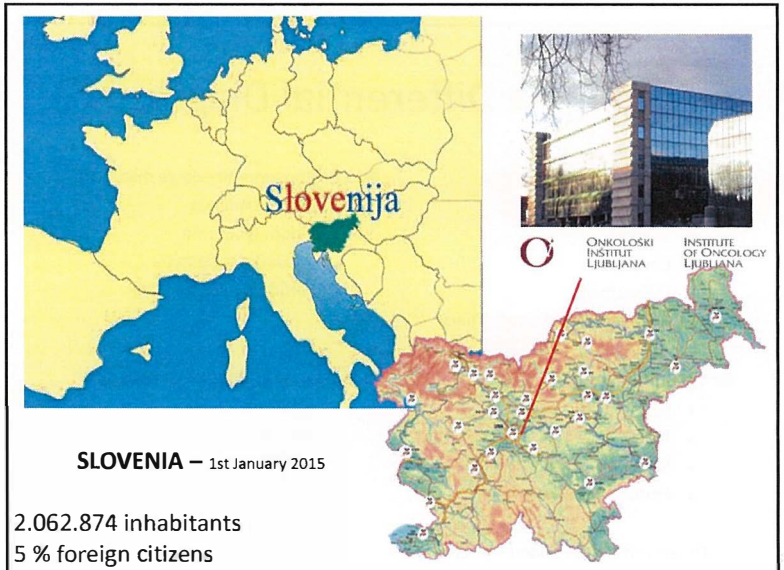
Cancer genetic counseling – from preventive medicine to treatment

Mateja Krajc

MANAGEMENT OF BRCA POSITIVE OVARIAN AND BREAST CANCER

7.4.2016



SLOVENIA – 1st January 2015

2.062.874 inhabitants
5 % foreign citizens

Battle For the Human Genome

Funded by the private company *Celera.*
Craig Venter

Funded by the USA's Human Genome Project
Francis Collins

This promises to be the fight of the millennium!!

CANCER AND THE HUMAN GENOME

- All cancers arise from genetic alterations

- **~5-10% of cases have a strong hereditary component**
- **~15-20% are "familial"/multifactorial**
- **~70-75% are thought to be sporadic**

- The Human Genome Project – by discovery of cancer genes developement of

  - Predictive genetic tests
  - Diagnostic tests
  - Therapies that target gene abnormailities in cancer cells

Forming a Differential Diagnosis

- Breast Cancer syndromes
  - BRCA1
  - BRCA2
  - Cowden
  - Li-Fraumeni
  - AT heterozygotes, and others
- Colon Cancer syndromes
  - FAP
  - HNPCC
  - Muir-Torre
  - Peutz-Jeghers, and others

Other: von Hippel-Lindau – VHL,...

- Chromosome Breakage disorders
  - Fanconi Anemia
  - Bloom syndrome
  - Ataxia-Telangiectasia
  - Xeroderma Pigmentosa
- Multiple Endocrine Neoplasias
  - MEN1
  - MEN2a
  - MEN2b
  - FMTC

American Society of Clinical Oncology (ASCO) 1996

Cancer predisposition testing be offered only when:

- Person has a strong family history of cancer or very early onset of the disease
- Test can be adequately interpreted
- Results will influence medical management of the patient or family member

Genetic cancer susceptibility testing

- can not be used as a screening test for general population!

- in clinical setting it is only one component of a comprehensive cancer **risk assessment/ therapeutic** plan

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HBOC in Slovenia (OIL)– management timeline

• 1999 - Genetic testing for *BRCA* genes available - with a close colaboration with VUB (Vrije Universiteit Brussel)

•2006 - cooperation established as well with The Royal Marsden NHS Foundation Trust, The Cyprus Institute of Neurology and Genetics

•2008 - all tests are performed at the Institute of Oncology Ljubljana (OI), state insurance covers the costs of counseling and testing when indicated

•2010 – organized screening for high risk at the OI

•2011 – clinical pathways established

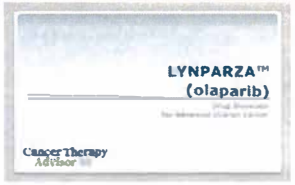
•2014 – urgent assessment (priority list) whenever needed for therapeutical purposes

Battle For the Human Genome

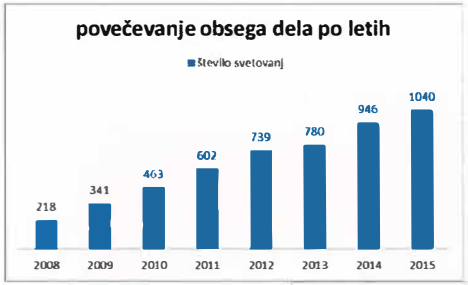
Craig Venter

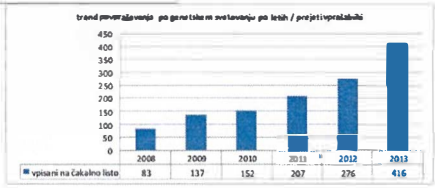
Francis Collins

This promises to be the light of the millennium!!



REFERRAL TREND





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REFERRALS

- ONCOLOGYST
- GYNECOLOGYST
- OTHER SPECIALIST
- BREAST UNITS
- SELFREFERRAL

- COUNSELING
- MULTIDISCIPLINARY ASSESSMENT
- TESTING
- FOLLOW – UP
- PROFILACTIC SURGERY
- TREATMENT

1999 - 2016

- 3138 individuals attended counseling
- 397 *BRCA* positive families

(1215 tested individuals from *BRCA*+ families)

- 348 high risk individuals sreened

at the follow-up clinic,
the rest are screened at their specialists

- 35 screen detected cancers

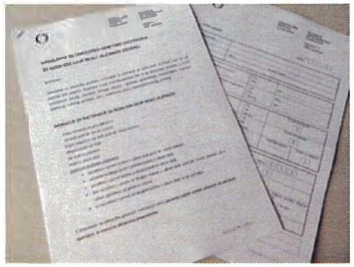
(breast and ovarian cancers)

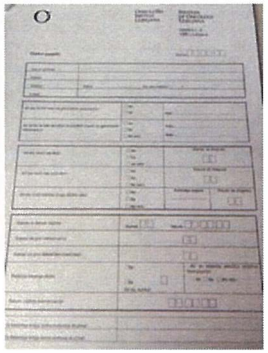
Clinical pathway, a multistep process

1. Identify at risk patient
2. Provide pre test counseling
3. Provide informed consent
4. Select and offer test
5. Disclose results
6. Provide post-test counseling and follow up

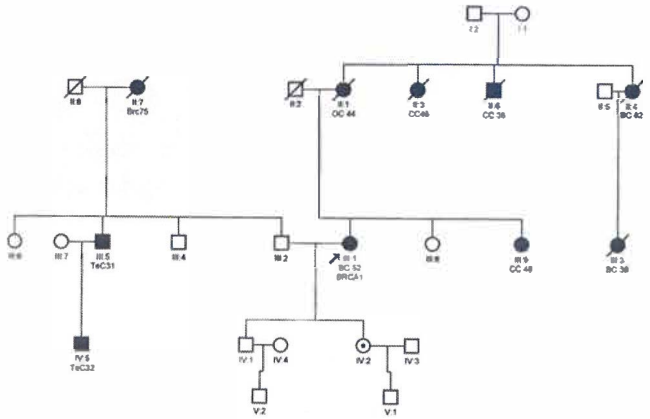
FIRST CONTACT WITH CANCER GENETIC COUNSELING SERVICE

Basic genetic counseling information leaflet and family history questionare





Family tree: when to susspect hereditary cancer syndrome



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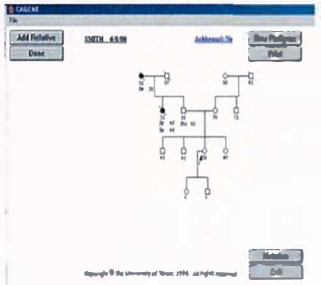
All cancer diagnosis are verified in the Cancer registry of the Republic of Slovenia

- one of the oldest population based **cancer registry** in Europe
- since 1950 – with obligatory reporting

Counseling About Risk

- Risk of having mutation in susceptibility gene vs. risk of developing cancer
- Patient's perception of risk
- Risk for patient's children / other family members

Probability of finding a mutation



2.0 BOADICEA risk calculation results

Index or subject of the BOADICEA calculation

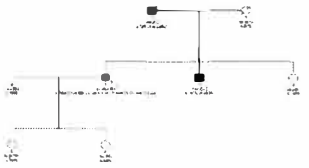
Forename identifier of index: natalia
Unique identifier of index: 1

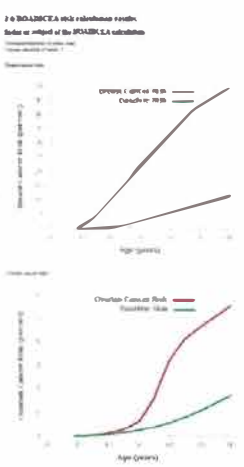
The BOADICEA model predicts the following BRCA1/BRCA2 mutation carrier probabilities and breast ovarian cancer risks for this individual

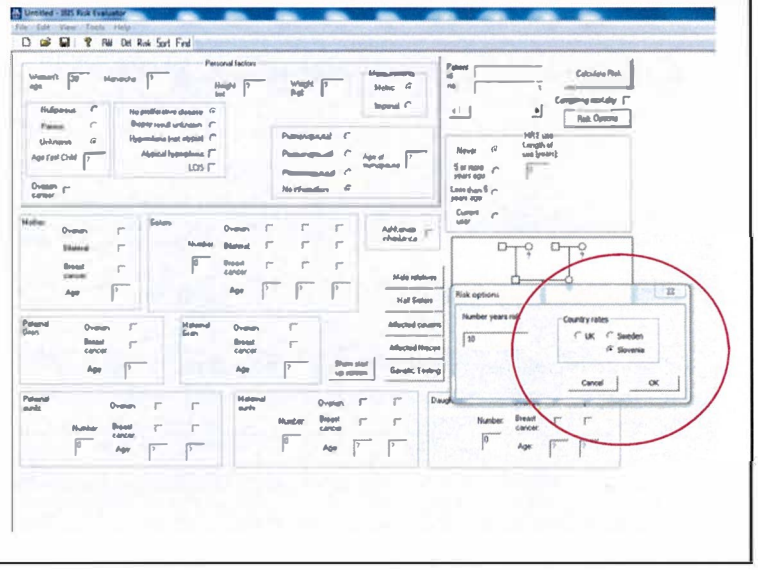
Genetic status	Mutation carrier probabilities (Percent)
BRCA1	2.4
BRCA2	68.0
No mutation	28.6

Cancer risks have not been computed

Model parameters	
Family member	natalia (1)
Mutation frequencies	UK BRCA1 6.3940e-4 BRCA2 0.00102
Mutation search sensitivities	Default BRCA1 0.7 BRCA2 0.5
Cancer incidence rates	UK







INDICATIONS FOR GENETIC COUNSELING

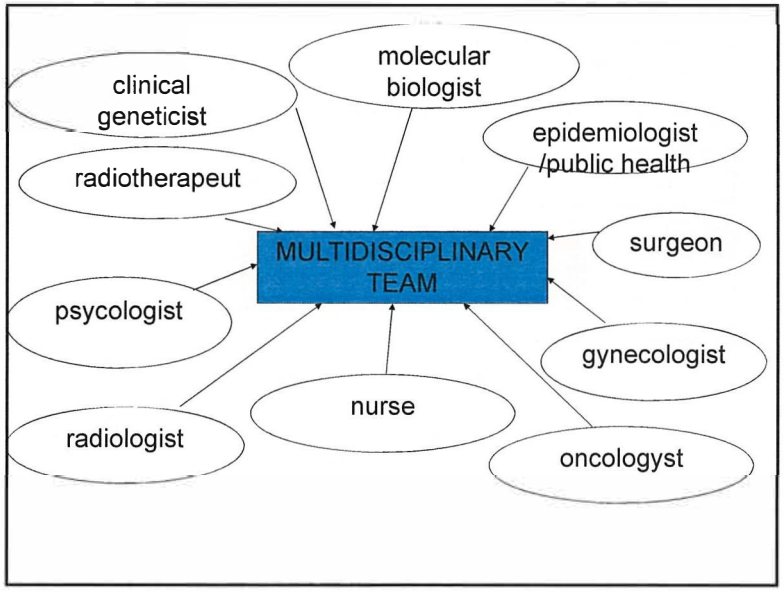
National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Genetic/Familial High-Risk Assessment: Breast and Ovarian

Version 2.2016
NCCN.org

Continue



Result disclosure

- Done in person
- After personal invitation letter, stating we have the result
- Individual always has an option not to come for "result session"

SURVEILLANCE/PROPHYLACTIC SURGERY

- **Offered at the insitute for *BRCA*+ patients**
- Dates for follow up are given from the cancer genetic office/clinic
- Follow up is centrally monitiored, perfomed at the institute of Oncology

***BRCA* Genetic testing provides the key for:**

Accurate cancer risk assessment

Effective genetic counseling

Appropriate medical follow-up

Appropriate treatment

Germline BRCA testing is moving from cancer risk assessment to a predictive biomarker for targeting cancer therapeutic, Moreno L. et al, ClinTransOncol, 2015

Results of genetic testing of ovarian cancer patients for BRCA status as a predictive biomarker for therapeutic approach – Slovenian experience

Mateja Krajc, Ana Blatnik, Vida Stegel, Petra Cerkovnik, Erik Škof and Srdjan Novaković

- PARP inhibitor was approved in Europe for *BRCA* mutation carriers as maintenance therapy in recurrent platinum sensitive OC
- In October 2014 we started offering *BRCA* tests to all OC patients as well as all fallopian tube and primary peritoneal serous carcinoma patients with high grade serous histology
- We tested all referred who attended genetic counseling and testing from October 2014 till October 2015
- Among first 114 referred patients 89/114 (78.1%) attended cancer genetic counseling and opted for *BRCA* testing
- **Mutation detection rate was 34.9%**

ABSTRACT POSTER PRESENTATION

ESO, CNIO and NRCO Conference on Familial Cancer, Madrid, 19-20 May 2016
Chairs: R. Eeles, UK - W. D. Foulkes, CA - M. Robledo, ES - H. Vasen, NL

CONCLUSIONS

- *BRCA* positive patients may benefit from targeted systemic therapy
- Their relatives may opt for testing and may benefit from surveillance and prevention strategies
- We must be prepared for high participation rates
- It is necessary to arrange adequate health resources to preserve the quality of *BRCA* genetic counseling and testing

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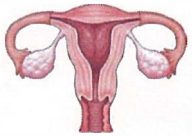
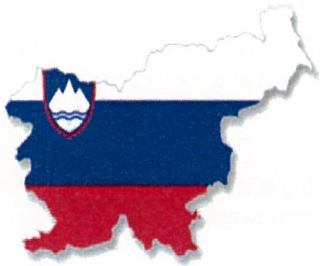
First Slovenian experiences with olaparib in treatment of ovarian cancer

Erik Škof
Medical oncologist
April 7th 2016



Ovarian cancer: Slovenija



- Incidence – 155*
- Median age – 60 years
- Stage of disease:
  - 75% advanced
    - (FIGO IIIC/IV)
- Histology
  - „High-grade" serous (75%),
- Frequent relapses (80%)
  - 5 y OS in SLO 43%*

* Cancer in Slovenia 2012

Background

- The HGS* is the most common histology type of ovarian cancer (75%)
- The probability for mutation of BRCA 1/2 genes in HGS* ovarian cancer is about 20%[1]
- Before september 2014 the aim of genetic testing for mutation of BRCA 1/2 genes was **prevention** of breast and ovarian cancer
- Regular monthly genetic multidisciplinary consilium (geneticist, medical oncologist, gynaecologist, surgeon, psychologist, head of molecular laboratory, etc.)
  - Indications for genetic testing

HGS* – high-grade serous

1. Zhang S, et al. Gynecol Oncol. 2011

Background

- Results of study 19 showed 7 months PFS* benefit of maintenance therapy with olaparib in patients with relapsed BRCA+ ovarian cancer[1].
- EMA approval of olaparib for relapsed BRCA+ ovarian cancer on 16/12/2014

PFS* – progression-free survival

1. Ledermann J et al, Lancet Oncol 2014

Ovarian cancer: Slovenija

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- Since september 2014:
  - All patients **with** HGS* cancer of ovaries, fallopian tubes or PPSC are offered to perform BRCA genetic testing **at diagnosis** (or at relapse)
  - The aim of BRCA genetic testing is **treatment with olaparib** not just prevention of breast and ovarian cancer
  - Active searching for BRCA+ patients (confidential data)

HGS* - high-grade serous

Zhang S, et al. Gynecol Oncol. 2011;121(2

Ovarian cancer: Slovenija

ONKOLOŠKI INŠTITUT LJUBLJANA — INSTITUTE OF ONCOLOGY LJUBLJANA

- Since september 2014:
  - The „need for speed" of BRCA testing results:
    - Medical oncologist recommends genetic counseling
    - Geneticist pretest counseling+ blood sample
    - Molecular lab. blood testing ⟶ results
    - Geneticist post test counseling
    - Medical oncologist therapy with olaparib

    <4 months
  - With NGS* results of BRCA testing in **2 months**
  - Waiting list for genetic counseling
    - „Highest-priority" patients with relapsed HGS** ovarian cancer
    - „High-priority" patients with HGS at diagnosis

NGS* - next generation sequencing
HGS** - high-grade serous

Olaparib experience in Slovenija

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- No clinical trial with olaparib in Slovenia ☹
- In september 2015 two patients started with olaparib maintenance treatment as a part of compassionate use programme ☺
- 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 ☺☺
- Label for olaparib is the same as in Study 19.
- At the moment there are 8 pts on therapy with olaparib
  - Range 1-7 months (median 2 months)
  - AE – mild nausea, fatigue
  - No progression of the disease

Availability of olaparib across the globe

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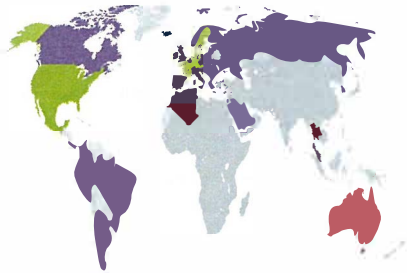


Now launched in 19 countries
US*, France, Germany, Luxembourg, Netherlands, Denmark, Norway, Finland, Sweden, Austria, Croatia, Mexico, Macau, UAE, Belgium, Spain, Israel, Switzerland, **SLOVENIA**

Approved in 22 countries
Bulgaria, Cyprus, Czech Republic, Estonia, Greece, Hungary, Ireland, Ireland, Italy, Korea, Latvia, Liechtenstein, Lithuania, Malta, Poland, Portugal, Romania, Slovakia, **Slovenia**, Ukraine and UK

Reviews ongoing in 12 countries
Argentina, Brazil, Saudi Arabia, Colombia, Hong Kong, Malaysia, Morocco, Singapore, Canada, Serbia, Panama and Russia

7 planned capsule submissions
Algeria, Camcar [CAMCAR Costa Rica; Ecuador; (Peru)]; Kuwait; Thailand and Tunisia

All approvals in BRCAm PSR maintenance except US* where Lynparza is approved in late line treatment

Surgical treatment of BRCA positive breast cancer patients - 15 years of Slovenian experiences

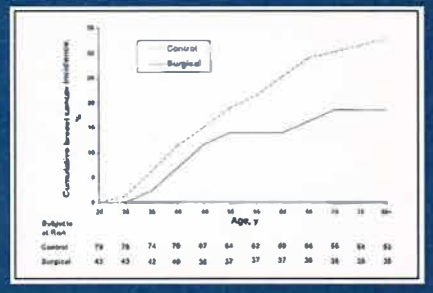
Janez Zgajnar
Institute of Oncology Ljubljana

Strategies in BRCA1/2 mutation carriers

- Intensive follow up
- Chemoprevention – (tamoxifen)
- Prophylactic surgery
  - Oophorectomy
  - Mastectomy
- Surgery in breast cancer patients

Risk Reduction by Oophorecomy

- 50% reduction in breast cancer risk
- 96% reduction in ovarian cancer risk
- Greater reduction if done early
- Benefits not negated by estrogen replacement therapy



Rebbeck TR. J Natl Cancer Inst 1999; 91:1475-9
Rebbeck TR. NEJM 2002;346:1616-22

Risk reducing salpingo-oophorectomy (RRSO)

Table 3. Hazard Ratio for the Development of *BRCA*-Associated Gynecologic Cancer After RRSO

Mutation	No. of Patients	No. of Women Electing RRSO	Mean FU (months)	No. of Gynecologic Cancers After RRSO	No. of Women Electing Surveillance	Mean FU (months)	No. of Gynecologic Cancers During Surveillance	Hazard Ratio	95% CI	P
BRCA1 and *BRCA2*	792	609	40.3	3	283	37.6	12	0.12	0.03 to 0.41	.001
BRCA1	498	325	41.1	1	173	40.1	10	0.15	0.04 to 0.56	.005
BRCA2	294	184	39.0	0	110	33.7	2	0.00	Not estimable	

Abbreviations: RRSO, risk-reducing salpingo-oophorectomy; FU, follow-up.

Table 4. Hazard Ratio for the Development of *BRCA*-Associated Breast Cancer After RRSO

Mutation	No. of Patients	No. of Women Electing RRSO	Mean FU (months)	No. of Breast Cancers After RRSO	No. of Women Electing Surveillance	Mean FU (months)	No. of Breast Cancers During Surveillance	Hazard Ratio	95% CI	P
BRCA1 and *BRCA2*	507	303	38.4	19	294	33.2	28	0.53	0.29 to 0.96	.036
BRCA1	369	190	36.3	15	179	34.6	19	0.61	0.30 to 1.22	.16
BRCA2	229	113	36.6	4	116	31.9	9	0.28	0.08 to 0.92	.036

Abbreviations: RRSO, risk-reducing salpingo-oophorectomy; FU, follow-up.

Kauff ND et al. JCO 2008;26:1331-7

Prophylactic bilateral mastectomy (PBM)

- At least 90% BC risk reduction
- Prospective study

76 pts after PBM	0 BC
63 pts of follow up	8 BC

p=0,003 (Meijers-Hejboer, NEJM 2001)

- Life years gained 2,9 - 5,3

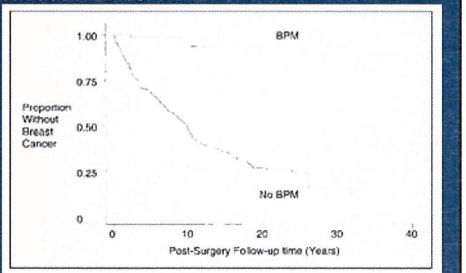
(Schrag et al, 1997)

PROSE study: bilateral prophylactic mastectomy

OUTCOME

2 breast cancers in the prophylactic group (both nipple-sparing): 1 nodal in BRCA 2,
1 residual breast in BRCA 1

90% risk reduction
7% risk to age 70



Rebbeck TR et al. JCO 2004;22:1055-62

Fig 1. Time to breast cancer diagnosis in female *BRCA1* mutation carriers with and without bilateral prophylactic mastectomy (BPM)

Prophylactic Mastectomy

ROTTERDAM FAMILY CANCER CLINIC

- 358 patients

	No breast cancer	Breast cancer
BRCA 1	115	76
BRCA 2	30	15
not tested	32	90

- Skin sparing mastectomy in all women
- 44% underwent salpingo-oophorectomy
- Median F/U: 4.5 years

OCCULT CANCERS

3 invasive, 5 DCIS **(2%)**

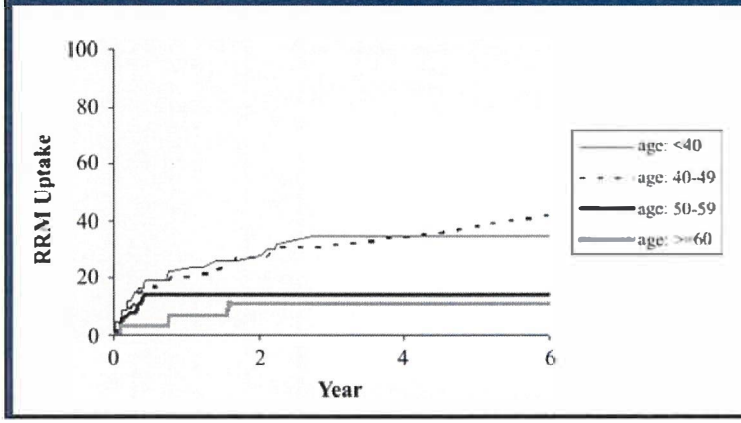
OUTCOME

0 breast cancer

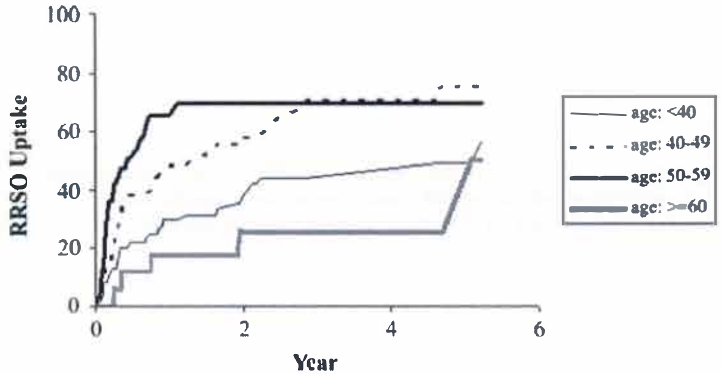
1 axillary metastasis
(1 year after mastectomy)

Heemskerk-Gerritsen BAM et al. Ann Surg Oncol 2007; 14:3335-44

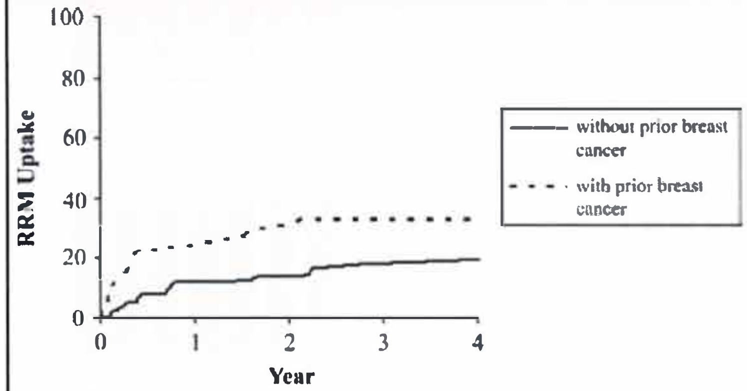
Beattie et al, Genetic testing and biomarkers, 2009



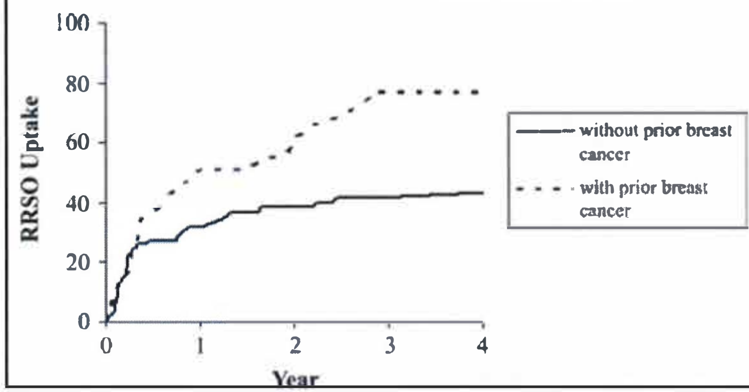
Beattie et al, Genetic testing and biomarkers, 2009



Beattie et al, Genetic testing and biomarkers, 2009



Beattie et al, Genetic testing and biomarkers, 2009



Metcalf et al, Int J Cancer, 2010

UPTAKE OF OPTIONS BY COUNTRY

Variables	Australia	Canada	France	Israel	Italy	Holland	Norway	Poland	U.S.A.	p Value
Prophylactic oophorectomy (n = 2,007)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Prophylactic mastectomy (n = 1,282)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible] (n = 1,133)	20 (100%)	[illegible]	3 (100%)	[illegible]	18 (100%)	37 (100%)	[illegible]	[illegible]	[illegible]	[illegible]
[illegible] (n = 1,134)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Tamoxifen/raloxifene (n = 1,134)	[illegible]	[illegible]	0 (0%)	[illegible]	0 (0%)	0 (0%)	0 (0%)	[illegible]	[illegible]	0.001

[1] All subjects.

[2] [illegible]

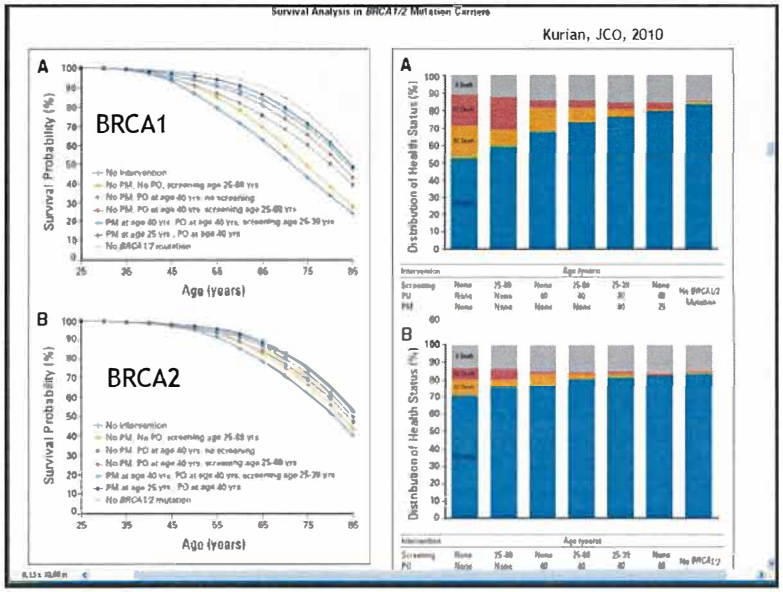
[3] [illegible]

[4] [illegible]

[5] [illegible]

UPTAKE OF AT LEAST ONE CANCER PREVENTION OPTION (PROPHYLACTIC MASTECTOMY, PROPHYLACTIC OOPHORECTOMY OR TAMOXIFEN) IN WOMEN WITHOUT BREAST CANCER

	Australia	Canada	France	Israel	Italy	Holland	Norway	Poland	USA
At least one cancer prevention option	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]



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Contralateral Prophylactic Mastectomy after Unilateral Breast Cancer: A Systematic Review & Meta-Analysis

Oluwadamilola M. Fayanju, MD[1], Carolyn R. T. Stolt, MPH[2], Susan Fowler, MLIS[3], Graham A. Colditz, DrPH[2], and Julie A. Margenthaler, MD[1]

CPM. We recommend that UBC patients without known elevated FGR be advised against CPM, while patients with elevated FGR should be advised that while CPM would significantly decrease their risk of MCBC, it is unlikely to prolong their lives.

The Breast Journal
ORIGINAL ARTICLE

Surgical Decision Making in the BRCA-Positive Population: Institutional Experience and Comparison with Recent Literature

Teresa Flippo-Morton, MD, FACS,* Kendall Walsh, CCRP,* Karim Chambers, MD,* Lisa Amacker-North, MS, CGC,† Brook White, MS, CGC,† Terry Saraniou, MD, FACS,* Danielle M. Boselli, MS,* 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
Uyei et al.	2006	37	24	57	27
Kram et al.	2006	43	19	NR	78
Friebel et al.	2007	537	21	38	55
Metcalfe 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	65
Garcia et al.	2013	305	44	NR	74
Flippo et al.	2014	87	44	41	46

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

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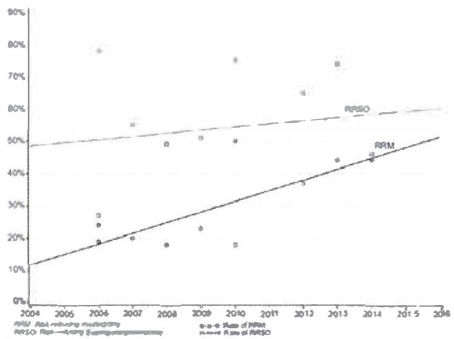


Figure 3. Rates of RRS uptake as reported in literature over time. Regression on time was significant for RRM (coeff: 3.24, p-value: 0.0287), and not for RRSO (coeff: 1.134, p-value: 0.6967).

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

PATIENTS INCLUDED

until end of 2015

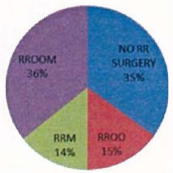
- FEMALE, BRCA 1 AND BRCA 2 MUTATION POSITIVE
- DATA AVAILABLE
- NO CANCER HISTORY (n= 174) OR
- BREAST CANCER AT ANY TIME (n=232)
- PATIENTS WITH OTHER CANCER TYPES WERE EXCLUDED

	N	%
PATIENTS WITH BREAST CANCER	232	100
NO RR SURGERY	81	35
RROO	35	15
RRM	33	14
RROOM	83	36

~ 65 % RISK REDUCING SURGERY

RRM 116/232 – 50%

PATIENTS WITH BC



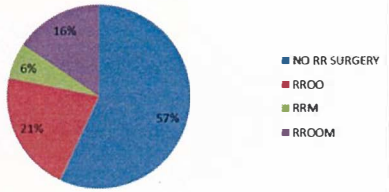
	N	%
PATIENTS WITHOUT ANY CANCER	174	100
NO RR SURGERY	99	57
RROO	37	21
RRM	11	6
RROOM	27	16

~ 40 % RISK REDUCING SURGERY

RRM 38/174 – 22%

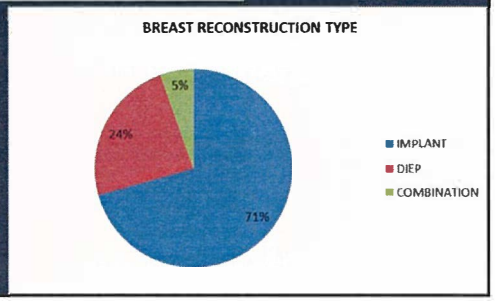
22/38 – 2013-15

PATIENTS WITHOUT ANY CANCER



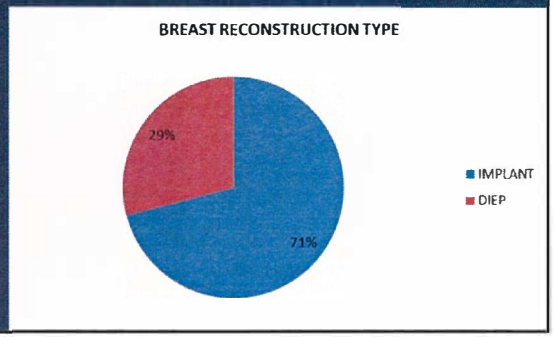
	N	%
PATIENTS WITH BREAST CANCER	116	100
NO RECONSTRUCTION	24	21
IMPLANT	65	56
DIEP	22	19
COMBINATION	5	4

~ 80 % BREAST RECONSTRUCTION RATE



	N	%
PATIENTS WITHOUT ANY CANCER	38	100
NO RECONSTRUCTION	7	18
IMPLANT	22	58
DIEP	9	24

~ 80 % BREAST RECONSTRUCTION RATE

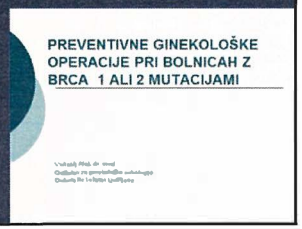


FALLOPIAN TUBE REMOVAL WITH PRESEVATION OF THE OVARIES

- 11 fallopian tube removals

  (in 7 cases a sinchronous bilateral mastectomy)

- Age from 30 to 40 years
  ~ 35,5 years



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 in our population is comparable to the data in the literature
- Patients at hereditary risk performing PM have a higher rate of immediate breast reconstruction compared to patients with sporadic BC

OUR (NEAR FUTURE) PLANS

- to include additional data in our database
- to analyse
  - the choice of risk reducing strategies by patients and the factors related to the choice
  - wheather the choice of risk reducing strategies varies by time and the factors related to the choice
  - Clinical outcomes of patients