MANAGEMENT OF BRCA POSITIVE OVARIAN AND BREAST CANCER

7.4.2016

Ljubljana, Hotel Union
SPEAKERS:

Prof. Gareth Evans, MD, PhD, Manchester Academic Health Science Centre, The University of Manchester, Central Manchester University Hospitals NHS Foundation Trust, Saint Mary’s Hospital, UK

Prof. Stan Kaye, MD, PhD, Professor of Medical Oncology, Royal Marsden NHS Foundation Trust, UK

Assist. Prof. Mateja Krajc, MD, PhD, Division of Cancer Genetic Counseling, Institute of Oncology Ljubljana, Slovenia

Prof. Srdjan Novaković, PhD, Division of Molecular Diagnostics, Institute of Oncology Ljubljana, Slovenia

Erik Škof, MD, PhD, Division of Medical oncology, Institute of Oncology Ljubljana, Slovenia

Prof. Janez Žgajnar, MD, PhD, Division of Surgery, Institute of Oncology Ljubljana, Slovenia

BOOKLET EDITOR:

Simona Borštnar, MD, PhD, Division of Medical Oncology, Institute of Oncology Ljubljana, Slovenia

ORGANIZERS AND PUBLISHERS:

Institute of Oncology Ljubljana
Slovenian Senologic Society

SPONSORS OF THE MEETING:

AstraZeneca
Roche

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 Novakovič
  • 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

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

Intracellular proteins involved in homologous recombination deficiency

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

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

Provides opportunity for selective treatment using PARP inhibitors

Poly(ADP-Ribose) Polymerase (PARP)

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

Binds directly to single strand breaks

Once bound to damaged DNA, PARP modifies itself producing DAD-ribosyl PARP — preventing large branched chains of Poly(ADP-ribose)

PARP inhibition and tumor-selective synthetic lethality

DNA damage (SSBs)

DNA replication (accumulation of DNA DSBs)

Normal cell with functional HR pathway

HR-mediated DNA repair

Cell survival

Impaired HR-mediated DNA repair (NHEJ etc.)

Cell death

Tumor-selective cytotoxicity

PS PARP inhibitors can also trap cytotoxic PARP-DNA complexes; clinical relevance unclear. 
Muse et al. Cancer Res. 2012 72 5388-5396

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%

BRCA1 germline mutation testing should be routine. Somatic testing too

Approx 50% of HGSOC could be candidates for PARPi

Olaparib, Chapter 1, 2005-9

Exquisite preclinical efficacy of PARPi in BRCA deficient ES cells

Phase I trial of KU559436 (olaparib) indicated excellent tolerance and expansion in 50 BRCA patients showed 46% response.


KU-0059481 IC50 = 3.4μM

KU-0058948 12.5-fold difference in IC50 between BRCA1-/- and +/-


Perry et al. J Clin Oncol, 2010; 28, 2512-2519

"this is nothing like chemotherapy"

Lesson 2 — listen to the patient
Olparib, a novel, orally active and well tolerated PARP inhibitor

- Olaparib (AZD2281; KU-0059436) 400 mg bd is the maximum tolerated dose with maximum PARP inhibition at 100 mg 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 in cohort expansion at 200 mg bd, with median response duration of 8 months.

<table>
<thead>
<tr>
<th>Correlation with platinum-free interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFI</td>
</tr>
<tr>
<td>&lt;0</td>
</tr>
<tr>
<td>0-4m</td>
</tr>
<tr>
<td>&gt;4m</td>
</tr>
<tr>
<td>Patient number total</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>24</td>
</tr>
<tr>
<td>13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECIST and/or CA125 or SD or PR, 100 mg bd</td>
</tr>
<tr>
<td>Percentage</td>
</tr>
<tr>
<td>25%</td>
</tr>
<tr>
<td>40%</td>
</tr>
<tr>
<td>35%</td>
</tr>
</tbody>
</table>

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

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

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?

Primary objective: compare efficacy of 2 dose levels of olaparib (300 mg and 400 mg bd) with liposomal doxorubicin (Caelyx)

- Efficacy of olaparib (400 mg bd) was as predicted, with response RECIST/CA125 in 59% and median PFS of 8.8 m.
- Olaparib (100 mg bd) had 33% RECIST/CA125 response, med PFS 6.5 m
- Caelyx was more effective than anticipated (response 39%; median PFS 7.5 m), thus no significant difference in primary end point
- HR 0.88, p = 0.66

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

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)

<table>
<thead>
<tr>
<th>33 pts at 400 mg bd</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECIST response</td>
</tr>
<tr>
<td>Clinical benefit</td>
</tr>
<tr>
<td>(incl. CA125 response)</td>
</tr>
<tr>
<td>11 (33%)</td>
</tr>
<tr>
<td>22 (66%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>24 pts at 100 mg bd</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECIST response</td>
</tr>
<tr>
<td>Clinical benefit</td>
</tr>
<tr>
<td>(incl. CA125 response)</td>
</tr>
<tr>
<td>3 (13%)</td>
</tr>
<tr>
<td>10 (42%)</td>
</tr>
</tbody>
</table>

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

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

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 platinum-based to which they had a maintained PR or CR prior to enrolment
- Stable CA-125

- Platinum status
  - Sensitive
  - Resistant

- RECIST
  - Sensitive 9/10 (90%)
  - Resistant 6/38 (16%)

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

Olaparib 400 mg po bid
Treatment until disease Progression

Primary end point: PFS

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

Study 19: Met PFS Primary Endpoint

<table>
<thead>
<tr>
<th></th>
<th>Olaparib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>8.4 mo</td>
<td>4.8 mo</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(7.4, 11.5)</td>
<td>(4.0, 5.3)</td>
</tr>
</tbody>
</table>

HR = 0.35 (95% CI: 0.25, 0.49); P<.00001

Analysis of Efficacy in maintenance study including BRCA WT

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

PFS in Patients With a BRCA Mutation*

<table>
<thead>
<tr>
<th>BRCAm (n = 138)</th>
<th>Olaparib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events: total patients (%)</td>
<td>26/74 (35.1)</td>
<td>46/62 (74.2)</td>
</tr>
<tr>
<td>Hazard PFS Hazard</td>
<td>3.2</td>
<td>4.3</td>
</tr>
<tr>
<td>95% CI (0.10, 0.31); P&lt;0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

Overall Survival in Patients With BRCA Mutation

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?

- 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

- 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

- 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

What other mechanisms of PARPi resistance may apply?

Resistance to PARP inhibitors

- 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.)

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 carboplatin to August 2002
- 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)
  - Reunited KU549436 (olaparib) in Phase 1 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

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)

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

- Total of 300 patients treated in 6 trials including:
  - Initial phase I/II trials
    - Randomised trial vs Caelyx
    - Bioavailability and scheduling studies
      - Capsule vs 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

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 (2 acute leukaemia, 1 MDS)
  - No difference in response between BRCA1 and 2

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:
  o SOLO 1 (n=344) – first line, platinum sensitive maintenance vs placebo g BRCAm pts only
  o SOLO 2 (n=264) – second line, platinum sensitive maintenance vs placebo g BRCAm pts only
  o SOLOist (n=157) – second line, platinum sensitive maintenance vs placebo in pts with HRD assoc or somatic BRCA m only.
  o SOLO 3 (n=411) – recurrent platinum sensitive, olaparib vs physician’s choice, g BRCAm patients only

Single agent activity for PARP inhibitors in ovarian cancer

<table>
<thead>
<tr>
<th>Drug</th>
<th>BRCA Mutation positive</th>
<th>BRCA wild type and unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib</td>
<td>n=300</td>
<td>70-100%</td>
</tr>
<tr>
<td></td>
<td>30-60%</td>
<td>7-10%</td>
</tr>
<tr>
<td>Rucaparib</td>
<td>30%</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>45%</td>
<td>15%</td>
</tr>
<tr>
<td>Niraparib</td>
<td>20%</td>
<td>5%</td>
</tr>
<tr>
<td>BMN 673</td>
<td>20%</td>
<td>5%</td>
</tr>
</tbody>
</table>

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

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

Homologous recombination deficiency (HRD) assay

- Do we have one?

- HRO 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

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

Homologous recombination deficiency (HRD) assay

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

- Do we have another?

Halusa 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 BRCA2 (4 somatic, 3 germ-line)
  - 4 ATM mutations
  - 3 other (FANCA/BRCA1; PALB2; HOAC2)
- Predictive accuracy of biomarker: 81%

Mateo et al, NCI 2015 373:1633-1638

PARP inhibitor — combination strategies

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

Pre-clinical and early clinical data with:

- Antiangiogenic agents¹
- P13K/AKT pathway inhibitors²
- Wee1 Kinase inhibitors³
- ATR inhibitors⁴

¹ Chan H & Bristow R, Clin Cancer Res. 2010 16:4553-60
**Antiangiogenic agents/PARP inhibitors**

- Complementary targets/mechanisms of action
- Potential enhancement of sensitivity to PARP 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.

**PARP inhibitor plus PI3K inhibitor**

- preclinical data in TNBC cells demonstrate that PI3K 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

**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 myelosuppression noted in first combination schedules, requiring dose reduction both of olaparib and chemotherapy.

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

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

<table>
<thead>
<tr>
<th>Maintenance olaparib 400mg bd until progression</th>
<th>Maintenance olaparib 400mg bd until progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 81</td>
<td>N = 81</td>
</tr>
<tr>
<td>Paclitaxel 175mg/m² Carboplatin AUC 4.8 olaparib 200mg bd for 10 days q 21</td>
<td>Paclitaxel 175mg/m² Carboplatin AUC 6 q 21</td>
</tr>
<tr>
<td>&lt; 6 months progression-free after last platinum</td>
<td>&lt; 6 = 55</td>
</tr>
</tbody>
</table>

Primary end point: PFS

BRCA mutation present (n = 41 patients). 20 olaparib, 21 control
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 3:1

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 PARP resistance be circumvented
   - novel inhibitors?
   - new combinations, e.g. with WEE-1 or ATR inhibitors?
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

• 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 2019

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

- BRCA1
- BRCA2

<table>
<thead>
<tr>
<th>4 Br/Ov</th>
<th>1 Ov</th>
<th>2 Ov</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>80%</td>
<td>90%</td>
<td>15%</td>
<td>80%</td>
</tr>
</tbody>
</table>

Population frequency and lifetime risk of breast cancer genes

- Lifetime risk for BRCA1, BRCA2, and BRCAAX
- Common variants: Small Effect Size
- Rare/Intermediate variants: Intermediate Effect Size
- Very rare variants: Large Effect Size
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

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

NHS funding at 10% threshold
Manchester scoring system

<table>
<thead>
<tr>
<th></th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC&lt;30</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>FBC 30-39</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>FBC 40-49</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>FBC 50-59</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>FBC&gt;59</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>MBC&lt;60</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>MBC&gt;59</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Ovarian cancer &lt;60</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Ovarian cancer &gt;59</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Prostate cancer &lt;60</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Prostate cancer &gt;59</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Total 230/1200 19

Assessment of score at 20% level

(Evans et al 2005)

<table>
<thead>
<tr>
<th>Combined score</th>
<th>Numbers</th>
<th>Percentage %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9</td>
<td>0/62</td>
<td>0</td>
</tr>
<tr>
<td>10-14</td>
<td>10/346</td>
<td>3.5</td>
</tr>
<tr>
<td>16-19</td>
<td>37/265</td>
<td>17</td>
</tr>
<tr>
<td>20-24</td>
<td>40/195</td>
<td>21</td>
</tr>
<tr>
<td>25-29</td>
<td>36/145</td>
<td>28</td>
</tr>
<tr>
<td>30-39</td>
<td>56/112</td>
<td>50</td>
</tr>
<tr>
<td>40+</td>
<td>51/81</td>
<td>85</td>
</tr>
<tr>
<td>Total</td>
<td>230/1200</td>
<td>19</td>
</tr>
</tbody>
</table>

ROC curve with path adjusted score at 20% combined

C statistic

0.74:0.78
**Pathology adjusted Manchester Score**

<table>
<thead>
<tr>
<th>Pathology</th>
<th>BRCA1 adj</th>
<th>BRCA2 adj</th>
</tr>
</thead>
<tbody>
<tr>
<td>Her2+</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>Lobular</td>
<td>-2</td>
<td>0</td>
</tr>
<tr>
<td>DCIS only</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>LCIS only</td>
<td>-4</td>
<td>0</td>
</tr>
<tr>
<td>Grade 1 IDC</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Grade 2 IDC</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3 IDC</td>
<td>+2</td>
<td>0</td>
</tr>
<tr>
<td>ER pos</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>ER neg</td>
<td>+1</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3 triple neg</td>
<td>+4</td>
<td>0</td>
</tr>
</tbody>
</table>

**Assessment of Manchester score at 10% level (update 2018)**

<table>
<thead>
<tr>
<th>Combined score</th>
<th>Ovarian (%)</th>
<th>Male Breast (%)</th>
<th>All families (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40+</td>
<td>99/130 (76)</td>
<td>13/13 (77)</td>
<td>114/156 (73)</td>
</tr>
<tr>
<td>40+ (confirmed oc)</td>
<td>73/86 (85)</td>
<td>5/13 (77)</td>
<td>77/156 (53)</td>
</tr>
<tr>
<td>35-39</td>
<td>34/62 (55)</td>
<td>8/12 (67)</td>
<td>66/113 (59)</td>
</tr>
<tr>
<td>30-36</td>
<td>44/66 (66)</td>
<td>8/13 (62)</td>
<td>88/119 (45)</td>
</tr>
<tr>
<td>25-29</td>
<td>74/187 (39.5)</td>
<td>4/20 (20)</td>
<td>124/404 (31)</td>
</tr>
<tr>
<td>20-24</td>
<td>76/138 (32)</td>
<td>6/19 (30)</td>
<td>148/669 (32)</td>
</tr>
<tr>
<td>15-19</td>
<td>26/197 (13)</td>
<td>3/20 (11)</td>
<td>94/193 (10)</td>
</tr>
<tr>
<td>12-14</td>
<td>19/145 (13)</td>
<td>1/11 (9)</td>
<td>31/179 (44)</td>
</tr>
<tr>
<td>&lt;12</td>
<td>9/90 (5.5)</td>
<td>0/4 (0)</td>
<td>16/674 (24)</td>
</tr>
<tr>
<td>Total</td>
<td>351/147 (30.5)</td>
<td>39/121 (28)</td>
<td>68/13535 (18)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Combined score</th>
<th>BRCA1 mut</th>
<th>BRCA2 mut</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3 (0)</td>
</tr>
<tr>
<td>10-19</td>
<td>7/117</td>
<td>2/117</td>
<td>9/117 (7.5)</td>
</tr>
<tr>
<td>15-19</td>
<td>13/110</td>
<td>9/110</td>
<td>22/110 (19)</td>
</tr>
<tr>
<td>20-24</td>
<td>28/92</td>
<td>6/92</td>
<td>34/92 (37)</td>
</tr>
<tr>
<td>25-29</td>
<td>22/60</td>
<td>8/60</td>
<td>30/60 (50)</td>
</tr>
<tr>
<td>30-39</td>
<td>31/45</td>
<td>5/45</td>
<td>36/45 (79)</td>
</tr>
<tr>
<td>40 +</td>
<td>20/25</td>
<td>3/25</td>
<td>23/25 (92)</td>
</tr>
<tr>
<td>Total</td>
<td>119/451</td>
<td>35/451</td>
<td>154/451 (38)</td>
</tr>
</tbody>
</table>

**TNT breast cancer**

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Age and selection</th>
<th>No tested</th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>Combined BRCA1 BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>POSH</td>
<td>UK</td>
<td>&lt; 41 sporadic</td>
<td>43</td>
<td>5 (11.3%)</td>
<td>0</td>
<td>5 (11.6%)</td>
</tr>
<tr>
<td>Manchester</td>
<td>UK</td>
<td>&lt; 31 unselected</td>
<td>30</td>
<td>11 (37%)</td>
<td>0</td>
<td>11 (37%)</td>
</tr>
<tr>
<td>FBCS</td>
<td>UK</td>
<td>&lt; 50 mixture</td>
<td>169</td>
<td>37 (22%)</td>
<td>0</td>
<td>37 (22%)</td>
</tr>
<tr>
<td>Gonzalez-Argolo</td>
<td>USA</td>
<td>Unselected</td>
<td>77</td>
<td>11 (14%)</td>
<td>3 (4%)</td>
<td>14 (16%)</td>
</tr>
<tr>
<td>Young</td>
<td>Canada</td>
<td>&lt;41 little or no FhX</td>
<td>54</td>
<td>5 (9%)</td>
<td>1 (2%)</td>
<td>6 (11%)</td>
</tr>
<tr>
<td>Corren</td>
<td>USA</td>
<td>Unselected</td>
<td>64</td>
<td>19 (30%)</td>
<td>6 (9%)</td>
<td>25 (39%)</td>
</tr>
</tbody>
</table>
Chance of BRCA1/2 in triple negative

- **No FH**
- one rel <50
- 2 rels <50

<table>
<thead>
<tr>
<th>Age in years</th>
<th>20-29</th>
<th>30-39</th>
<th>40-49</th>
<th>50-59</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chance (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td>60</td>
<td>50</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>30-39</td>
<td>55</td>
<td>45</td>
<td>35</td>
<td>25</td>
</tr>
<tr>
<td>40-49</td>
<td>50</td>
<td>40</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>50-59</td>
<td>45</td>
<td>35</td>
<td>25</td>
<td>15</td>
</tr>
</tbody>
</table>

Genetic testing for ovarian cancer

- Exclude borderline and mucinous ovarian tumours
- Alisp et al 2012 Journal of clinical oncology
- 1,001 sequentially diagnosed epithelial ovarian cases
- 14% patients had BRCA1/2 germline mutation
  - 22.4% high grade serous
  - 8.4% endometrioid
  - 6% in clear cell (but pathology review reclassified 3/4 as high grade serous)
  - 0 in carcinosarcomas
  - diagnosed 61+ with no PSYH1, 10/250 (6.4%)-personal comm Mitchell G
What can all be tested at 10%

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

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 categories
  - e.594-2A>C reclassified from actionable to poly.

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

IARC classification

Proposed Classification System for Sequence Variants Identified by Genetic Testing

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Probability of being Pathogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Definitely Pathogenic</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>4</td>
<td>Likely Pathogenic</td>
<td>0.95-0.99</td>
</tr>
<tr>
<td>3</td>
<td>Uncertain</td>
<td>0.05-0.949</td>
</tr>
<tr>
<td>2</td>
<td>Likely Not Pathogenic or of Little Clinical Significance</td>
<td>0.001-0.049</td>
</tr>
<tr>
<td>1</td>
<td>Not Pathogenic or of No Clinical Significance</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
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
- Potential to maintain/ increase anxiety about own/other's risk
- Limited/radical preventive options
- Sarcasmally 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%

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

<table>
<thead>
<tr>
<th>Cancer risk to age</th>
<th>BRCA1 Breast</th>
<th>BRCA2 Breast</th>
<th>BRCA1 Ovary</th>
<th>BRCA2 Ovary</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>3%</td>
<td>4%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>40</td>
<td>21%</td>
<td>21%</td>
<td>3.7%</td>
<td>0</td>
</tr>
<tr>
<td>50</td>
<td>44%</td>
<td>51%</td>
<td>21%</td>
<td>4.5%</td>
</tr>
<tr>
<td>60</td>
<td>63%</td>
<td>71%</td>
<td>44.5%</td>
<td>18%</td>
</tr>
<tr>
<td>70</td>
<td>75% (72-78)</td>
<td>80% (77-83)</td>
<td>61% (58-64)</td>
<td>33% (29-37)</td>
</tr>
<tr>
<td>80</td>
<td>85% (82-88)</td>
<td>90% (87-93)</td>
<td>65% (62-68)</td>
<td>38% (34-42)</td>
</tr>
</tbody>
</table>
Cumulative risk of breast cancer by age cohort for BRCA1 and BRCA2 combined.

One Minus Survival Functions

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

- BRCA1 588 kindred
  - 58 185 del AG (10%)
  - 49 4184 del4 (8%)
  - 29 5503C>T (5%)
  - 25 546G>T (4%)
  - 24 5382 delC (4%)
  - 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

<table>
<thead>
<tr>
<th>Gene</th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>250</td>
<td>236</td>
</tr>
<tr>
<td>Median age</td>
<td>36.9</td>
<td>40.8</td>
</tr>
<tr>
<td>RRMM</td>
<td>81</td>
<td>53</td>
</tr>
<tr>
<td>Occult BC at RRMM</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>BC in follow up</td>
<td>13 (15)</td>
<td>18 (19)</td>
</tr>
<tr>
<td>Years follow up</td>
<td>1054.58</td>
<td>1044.46</td>
</tr>
<tr>
<td>Rate</td>
<td>14.2 per 1000</td>
<td>18.2 per 1000</td>
</tr>
</tbody>
</table>

Lead time

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.
### 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).
Other prospective studies-EMBRACE  
Mavadatt 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.

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 - BC proven carriers and FDRs

Survival from diagnosis (1980+)- BC
Survival from 5yrs post diagnosis - BC

Survival Functions

247:211
10yr survival
74% vs 56%
P=0.0037

Effect of contralateral RRM - Ingham et al BCRT 2013

Effect of contralateral RRM - 105 cases and controls

Hazard ratio 0.37 (95%CI 0.174-0.798); p=0.008
17 deaths in no CRRM group had CBC

Effects of RRS on BRCA1/2 before cancer

R =0.09; 95%CI 0.04-0.29
BRCA1/2 carriers – risk reducing surgery

HR = 0.09; 95%CI 0.04-0.29

No surgery 460
Any true surgery 232

56 RRM only
68 RRM + BSO
108 BSO only

Number at risk
No surgery 460
Any true surgery 232

HR 0.25 95%CI 0.1-0.59

56 RRM only
68 RRM + BSO
108 BSO only

Number at risk
No Surgery 460
Any true surgery 232

Effects of RRS on BRCA1/2 before cancer

Ngham et al Breast Cancer Res Treat 2013

Chemoprevention
Prevention trials - recruitment periods

- Exemestane v placebo
- Anastrozole v placebo
- Raloxifene v tamoxifen
- Raloxifene v placebo

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen v placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBIS I</td>
<td>7,140</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italian</td>
<td>5,408</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSABP P1</td>
<td>13,388</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Royal Marsden</td>
<td>2,471</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP I</td>
<td>4,950</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP II</td>
<td>3,864</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RUTH 10,101</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MORE</td>
<td>7,745</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CORE</td>
<td>3,510</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Disease Prevention: SERMs & Aromatase Inhibitors

- IBIS II (Anastrozole)
- MAP 3 (Exemestane)
- Royal Marsden
- NSABP-P1
- Italian
- IBIS-1
- All tamoxifen prevention
- CORE (Raloxifene)
- RUTH (Raloxifene)
- STAR (Rat v tam)

Aromatase inhibitors better than tamoxifen - contralateral breast

- Adjuvant tamoxifen v placebo
- Adjuvant tamoxifen v AI

Reduction in contralateral new primary
Contralateral Breast Cancers in Aromatase Adjuvant Trials

Contralateral Breast Cancers in Aromatase Adjuvant Trials

- ATAC
- Italian
- MA-17
- IES
- ARNO/ABCSG
- BIG 1-98
- Combined

Odds ratio (log scale)

Future potential agents

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

Survival in MRI screened BRCA1/2

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>Number at risk</th>
<th>Number of events</th>
<th>% Overall survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>No-screening</td>
<td>5-year</td>
<td>320</td>
<td>59</td>
<td>86.7 (83.6 - 90.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10-year</td>
<td>172</td>
<td>101</td>
<td>73.7 (69.3 - 78.4)</td>
</tr>
<tr>
<td>G2</td>
<td>Mammogram</td>
<td>5-year</td>
<td>35</td>
<td>4</td>
<td>90.7 (82.4 - 99.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10-year</td>
<td>18</td>
<td>5</td>
<td>87.7 (78.0 - 98.5)</td>
</tr>
<tr>
<td>G3</td>
<td>Mammogram + MRI</td>
<td>5-year</td>
<td>35</td>
<td>2</td>
<td>95.3 (89.3 - 100.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10-year</td>
<td>23</td>
<td>2</td>
<td>95.3 (89.3 - 100.0)</td>
</tr>
</tbody>
</table>
Survival in MRI screened BRCA1/2

MRI Screening in BRCA2 carriers (UK-Norwegian)

**Nice: Key Screening Recommendations 2013**

**Survival 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

Acknowledgments

- Manchester
- Fiona Laloo
- Andrew Shenton
- Lesley Lorimer
- Judy Collins
- Edinburgh
- Diane Stirling
- Mary Porteous
- Michael Steel

- Oslo
- Søl Møller
- Lovise Mæhle
- Anne Dørum
- Bergen
- Jaran Apold
- Leiden
- Christi van Asperen
- Katja Gaarenstroom

- Genetic register
- Gareth Evans
- Dr Fiona Laloo
- Dr Bronwyn Kerr
- Marion MacAllister
- Rachel Beik
- Tara Clancy
- Andrew Shenton
- Cancer register
- Dr. Tony Moran
- Psychiatry
- Penny Hopwood

- Family History Clinic (breast)
- Prof Anthony Howell
- Dr Andrew Maurice
- Radiology
- Dr Sylvia Rimmer
- Dr Sarah Russell
- Lesley Lorimer
- Judy Collins
- Gynaecology/Oncology
- Paul Donnai, Rick Clayton
- Mourad Seiel
- Gordon Jayson, Andrew Clamp
BRCA genes and genes beyond BRCA — genetic testing from germline to somatic mutations - laboratory experiences

Srdjan Novaković

INDICATIONS FOR CLINICAL TESTING

BRCA-Related Breast and/or Ovarian Cancer Syndrome

BRCA1 TESTING CRITERIA

- Indicated for a family with a known autosomal recessive BRCA1/BRCA2 gene mutation
- Personal history of breast cancer with one or more of the following:
  - Diagnosis before age 35
  - Diagnosis before age 40 with ≥ 2 first-degree relatives with breast cancer primary
  - ≥ 2 first-degree relatives with breast cancer at any age
  - ≥ 2 first-degree relatives with pancreatic cancer
  - ≥ 2 first-degree relatives with prostate cancer (Gleason score ≥ 7) at any age
- An unexplained in familial history
- Triplet negative breast cancer
- Diagnosis at any age with:
  - ≥ 2 first-degree relatives with breast cancer diagnosed before age 50
  - ≥ 2 first-degree relatives with breast cancer at any age
- ≥ 2 first-degree relatives with ovarian cancer at any age

BRCA2 TESTING CRITERIA

- Personal history of prostate cancer (Gleason score ≥ 7) at any age with ≥ 2 first-degree relatives with breast cancer primary at any age
- Personal history of prostate cancer at any age with ≥ 2 first-degree relatives with breast cancer at any age
- Personal history of prostate cancer at any age with ≥ 2 first-degree relatives with breast cancer at any age
- Personal history of prostate cancer at any age with ≥ 2 first-degree relatives with breast cancer at any age
- Personal history of prostate cancer at any age with ≥ 2 first-degree relatives with breast cancer at any age

CANCER FAMILY SYNDROMES ASSOCIATED WITH BRCA

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

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)
### RESULTS OF BRCA1/2 MUTATION SCREENING 1999 - DECEMBER 2015

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

#### BRCA1/2 MUTATION DISTRIBUTION FREQUENCY

All together 355 BRCA1/2 positive families

<table>
<thead>
<tr>
<th>NO. OF MUTATIONS</th>
<th>NO. OF FAMILIES</th>
<th>OVERALL RELATIVE FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>IN 3 FAMILY ONLY</td>
<td>47</td>
<td>13.24</td>
</tr>
<tr>
<td>IN 3-10 FAMILIES</td>
<td>24</td>
<td>25.35</td>
</tr>
<tr>
<td>IN 11-20 FAMILIES</td>
<td>4</td>
<td>16.62</td>
</tr>
<tr>
<td>IN &gt;20 FAMILIES</td>
<td>4</td>
<td>44.79</td>
</tr>
</tbody>
</table>

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

Mutation detection rate: 22.6% (355/1567)

### BRCA1 AND BRCA2 SCREENING STRATEGY 1999-2015

- **Unknown mutation in the family**
  1. Testing for the most common mutations in Slovene population
  2. MSH detection of large rearrangements

- **Known mutation in the family**
  1. We issue a report with an expert opinion whether the specific mutation is present in the patient blood sample or not.
  2. The report is informative when a mutation is detected.
  3. The report is noninformative if the mutation is not detected.
The report is informative when a mutation is proven.

The report is noninformative if the mutation is not detected.

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
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.

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

---

**BRCA1/2 Mutation Spectrum 1995 - 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.

### Most Common BRCA1/2 Mutations in Breast or Ovarian Cancer Patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>2 the most common mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>BRCA1 c.181T&gt;G (p.Cys61Gly), BRCA1 c.1687C&gt;T (p.Gln563*).</td>
</tr>
<tr>
<td>Breast + ovarian cancer</td>
<td>BRCA1 c.181T&gt;G (p.Cys61Gly), BRCA1 c.1687C&gt;T (p.Gln563*).</td>
</tr>
<tr>
<td>Ovarian + endometrial cancer</td>
<td>BRCA1 c.181T&gt;G (p.Cys61Gly), BRCA1 c.1687C&gt;T (p.Gln563*).</td>
</tr>
</tbody>
</table>

### 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

<table>
<thead>
<tr>
<th>Gene</th>
<th>No. of patients</th>
<th>%</th>
<th>No. Of different mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>47</td>
<td>78.33%</td>
<td>21</td>
</tr>
<tr>
<td>BRCA2</td>
<td>13</td>
<td>21.66%</td>
<td>10</td>
</tr>
<tr>
<td>BRCA1/2</td>
<td>60</td>
<td>100%</td>
<td>31</td>
</tr>
</tbody>
</table>

* In a single patient the mutation in BRCA2 and in ATM was detected at the same time.
Genetic testing of BRCA genes provides the key to:

- Accurate cancer risk assessment
- Effective genetic counseling
- Appropriate medical follow-up
- Appropriate treatment
Cancer genetic counseling – from preventive medicine to treatment

Mateja Krajc

MANAGEMENT OF BRCA POSITIVE OVARIAN AND BREAST CANCER

7.4.2016

Battle For the Human Genome

This promises to be the fight of the millennium!!

Newsweek

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 development of

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

SLOVENIA – 1st January 2015

2,062,874 inhabitants
5% foreign citizens
Forming a Differential Diagnosis

- Breast Cancer syndromes
  - BRCA1
  - BRCA2
  - Cowden
  - Li-Fraumeni
  - AT heterozygotes, and others

- Chromosome Breakage disorders
  - Fanconi Anemia
  - Bloom syndrome
  - Ataxia-Telangiectasia
  - Xeroderma Pigmentosa

- Colon Cancer syndromes
  - FAP
  - HNPCC
  - Muir-Torre
  - Peutz-Jeghers, and others

- Multiple Endocrine Neoplasias
  - MEN1
  - MEN2a
  - MEN2b
  - FMTC

Other: von Hippel-Lindau – VHL...

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

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

HBOC in Slovenia (OIL) – management timeline
- 1999 - Genetic testing for BRCA genes available – with a close collaboration 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 (OIL), 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

LYNPARZA™
(olaparib)

INSTITUTE OF ONCOLOGY LJUBLJANA

- ONCOLOGIST
- GYNECOLOGIST
- OTHER SPECIALIST
- BREAST UNITS
- SELFREFERRAL

1999 - 2016
- 3138 individuals attended counseling
- 397 BRCA positive families
  (1215 tested individuals from BRCA+ families)
- 348 high risk individuals screened 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 questionnaire

ONKOLOŠKI INŠTITUT LJUBLJANA

Institute of Oncology

Ljubljana

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

Family tree: when to suspect hereditary cancer syndrome

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

The BOADICEA model predicts the influence of BRCA1 and BRCA2 mutations on cancer probabilities and provides risk estimates for the individual.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutation</th>
<th>Cancer risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>84.2%</td>
<td>1.6%</td>
</tr>
<tr>
<td>BRCA2</td>
<td>84.2%</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

INDICATIONS FOR GENETIC COUNSELING

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)
Genetic/Familial
High-Risk Assessment: Breast and Ovarian
NCCN.org
**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 institute for BRCA+ patients
- Dates for follow up are given from the cancer genetic office/clinic
- Follow up is centrally monitored, performed 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

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

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

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 Novakovic

- 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, ESMO and ERCO Conference on Familial Cancer, Madrid, 19-20 May 2016
Authors: B. Tane, UK - W. D. Fodden, CA - M. Kaplan - E. S. N.
First Slovenian experiences with olaparib in treatment of ovarian cancer

Erik Škof
Medical oncologist
April 7th 2016

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

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%*

Results of study 19 showed 7 months PFS* benefit of maintenance therapy with olaparib in patients with relapsed BRCA+ ovarian cancer\(^2\).

EMA approval of olaparib for relapsed BRCA+ ovarian cancer on 16/12/2014

* Cancer in Slovenia 2012

\(^1\) Zhang, et al. Gynecol Oncol. 2001
**Ovarian cancer: Slovenija**

- Since September 2014:
  - All patients with HGS* cancer of ovaries, fallopian tubes or PPSC are offered to perform BRCA genetic testing at diagnosis (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).

**Olaparib experience in Slovenija**

- 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**

- Now launched in 19 countries: Argentina, Brazil, Saudi Arabia, Colombia, Hong Kong, Malaysia, Morocco, Singapore, Canada, Serbia, Pakistan and Russia.
- Approved in 22 countries: America, Australia, Brazil, Canada, Denmark, France, Germany, Israel, Italy, Japan, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, UK, and Ukraine.
- 7 planned capsule submissions: Argentina, Brazil, Saudi Arabia, Colombia, Hong Kong, Malaysia, Morocco, Singapore, Canada, Serbia, Pakistan and Russia.

---

*HGS*: High-grade serous.
Surgical treatment of BRCA positive breast cancer patients - 15 years of Slovenian experiences

Risk Reduction by Oophorectomy

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

Risk reducing salpingo-oophorectomy (RRSO)

Strategies in BRCA1/2 mutation carriers

- Intensive follow up
- Chemoprevention – (tamoxifen)
- Prophylactic surgery
  - Oophorectomy
  - Mastectomy
- Surgery in breast cancer patients
Beattie et al, Genetic testing and biomarkers, 2009

**BRSO Uptake**

- age < 40
- age: 40-49
- age: 50-59
- age: ≥ 60

**Year**

0 2 4 6

0 20 40 60 80 100

Beattie et al, Genetic testing and biomarkers, 2009

**BRM Uptake**

- without prior breast cancer
- with prior breast cancer

**Year**

0 1 2 3 4

0 20 40 60 80 100

Beattie et al, Genetic testing and biomarkers, 2009

**BRSO Uptake**

- without prior breast cancer
- with prior breast cancer

**Year**

0 1 2 3 4

0 20 40 60 80 100

Beattie et al, Genetic testing and biomarkers, 2009

**UPTAKE OF OPTIONS BY COHORT**

<table>
<thead>
<tr>
<th>Variables</th>
<th>without prior breast cancer</th>
<th>with prior breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRSO Uptake</td>
<td>100% (95% CI: 88-100%)</td>
<td>100% (95% CI: 88-100%)</td>
</tr>
<tr>
<td>BRM Uptake</td>
<td>100% (95% CI: 88-100%)</td>
<td>100% (95% CI: 88-100%)</td>
</tr>
</tbody>
</table>

---

1. All schools.
2. Alpha: 0.05. Se reported where data on differences were available.
3. Alpha: 0.01. Se reported where data on differences were available.
4. Alpha: 0.001. Se reported where data on differences were available.
5. Alpha: 0.0001. Se reported where data on differences were available.
6. Alpha: 0.00001. Se reported where data on differences were available.
7. Alpha: 0.000001. Se reported where data on differences were available.
8. Alpha: 0.0000001. Se reported where data on differences were available.
9. Alpha: 0.00000001. Se reported where data on differences were available.
Table 2. Reported Rates of Uptake of RRS in the BRCA-Positive Population in Current Literature

<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
<th>Sample size</th>
<th>% RRm</th>
<th>% Surveillance</th>
<th>% RRSO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uyel et al.</td>
<td>2006</td>
<td>37</td>
<td>24</td>
<td>57</td>
<td>27</td>
</tr>
<tr>
<td>Kram et al.</td>
<td>2006</td>
<td>43</td>
<td>19</td>
<td>NR</td>
<td>78</td>
</tr>
<tr>
<td>Field et al.</td>
<td>2007</td>
<td>537</td>
<td>21</td>
<td>38</td>
<td>55</td>
</tr>
<tr>
<td>Metcalfe et al.</td>
<td>2008</td>
<td>1,383</td>
<td>18</td>
<td>NR</td>
<td>49</td>
</tr>
<tr>
<td>Beanie et al.</td>
<td>2009</td>
<td>272</td>
<td>23</td>
<td>NR</td>
<td>51</td>
</tr>
<tr>
<td>Korea et al.</td>
<td>2010</td>
<td>31</td>
<td>18</td>
<td>82</td>
<td>18</td>
</tr>
<tr>
<td>Skye et al.</td>
<td>2010</td>
<td>306</td>
<td>50</td>
<td>NR</td>
<td>75</td>
</tr>
<tr>
<td>Schwarz et al.</td>
<td>2012</td>
<td>144</td>
<td>37</td>
<td>NR</td>
<td>86</td>
</tr>
<tr>
<td>Garcia et al.</td>
<td>2013</td>
<td>305</td>
<td>44</td>
<td>NR</td>
<td>74</td>
</tr>
<tr>
<td>Filippo et al.</td>
<td>2014</td>
<td>87</td>
<td>44</td>
<td>41</td>
<td>46</td>
</tr>
</tbody>
</table>

NR, not reported; RRm, risk-reducing mastectomy; RRSO, risk-reducing salpingo-oophorectomy.

Figure 3. Rates of RRS uptake as reported in literature by year. Regression on time was significant for RRm (coeff: 3.24, p-value: 0.0297), and not for RRSO (coeff: 1.134, p-value: 0.8967).

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.
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

<table>
<thead>
<tr>
<th>PATIENTS WITH BREAST CANCER</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO RR SURGERY</td>
<td>81</td>
<td>35</td>
</tr>
<tr>
<td>RROO</td>
<td>35</td>
<td>15</td>
</tr>
<tr>
<td>RRM</td>
<td>33</td>
<td>14</td>
</tr>
<tr>
<td>RROOM</td>
<td>83</td>
<td>36</td>
</tr>
</tbody>
</table>

~ 65 % RISK REDUCING SURGERY

<table>
<thead>
<tr>
<th>PATIENTS WITHOUT ANY CANCER</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO RR SURGERY</td>
<td>99</td>
<td>57</td>
</tr>
<tr>
<td>RROO</td>
<td>37</td>
<td>21</td>
</tr>
<tr>
<td>RRM</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>RROOM</td>
<td>27</td>
<td>16</td>
</tr>
</tbody>
</table>

~ 40 % RISK REDUCING SURGERY

RRM 116/232 = 50%

RRM 38/174 = 22%

22/38 = 2013-15
Patients with breast cancer

<table>
<thead>
<tr>
<th>BREAST RECONSTRUCTION TYPE</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
</table>
| NO RECONSTRUCTION          | 24 | 21%
| IMPLANT                    | 65 | 56%
| DIEP                       | 22 | 19%
| COMBINATION                | 5  | 4% |

Patients without any cancer

<table>
<thead>
<tr>
<th>BREAST RECONSTRUCTION TYPE</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
</table>
| NO RECONSTRUCTION          | 7  | 18%
| IMPLANT                    | 22 | 58%
| DIEP                       | 9  | 24%

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.

Fallopian tube removal with preservation of the ovaries

- 11 fallopian tube removals (in 7 cases a synchronous bilateral mastectomy)
- Age from 30 to 40 years ~ 35.5 years
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
  - whether the choice of risk reducing strategies varies by time and the factors related to the choice
  - Clinical outcomes of patients