Evolution of genetic counselling for hereditary ovarian cancer

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Addenbrooke’s Hospital
Cambridge
Overview

• Traditional models of genetic testing & counselling for hereditary ovarian cancer

• Changes to service delivery

• Genetic Counsellors and mainstreaming

• Broader panel testing and family implications
Typical referrals to a Cancer Genetics clinic

- Colorectal
- Rare syndromes
- Breast/ovary
- Other
Referral to Clinical Genetics based on age + FHx criteria

Minority of families

~3 months

Seen in outpatients genetics clinic, pre-test BRCA1/2 consent app’t

~3 months

Result given by Clinical Genetics

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**Previous model**

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**Referral to Clinical Genetics based on age + FHx criteria**

Minority of families

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Seen in outpatients genetics clinic, pre-test BRCA1/2 consent app’t

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Result given by Clinical Genetics

---

**BRCA1 and BRCA2 mutation testing criteria**

**Key**
- BC: Breast cancer
- PC: Prostate cancer
- OC: Ovarian cancer
- PanC: Pancreatic cancer
- MBC: Male breast cancer
- FDR: First degree relative

**A woman with breast cancer who...**
1. has bilateral BC and both diagnosed <50
2. has triple negative BC diagnosed <60
3. has BC diagnosed <30
4. also has OC
5. has bilateral BC and a relative with BC <60
6. has a relative with BC and both diagnosed <45
7. has relatives with cancer and a Manchester score ≥ 15

**A woman with ovarian cancer who...**
1. has OC <70
2. also has BC
3. has OC >70 and a relative with OC or BC

**A man with breast cancer who...**
1. has BC <60
2. has a relative with OC or MBC
3. has relatives with cancer and a Manchester score ≥ 15

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**Family Tree**

- OvCa dx 55
- BrCa dx 50
- BrCa dx 41
- BrCa
Improved access
Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer


BACKGROUND
Most women with newly diagnosed advanced ovarian cancer have a relapse within 3 years after standard treatment with surgery and platinum-based chemotherapy. The benefit of the oral poly(adenosine diphosphate-ribose) polymerase inhibitor olaparib in relapsed disease has been well established, but the benefit of olaparib as maintenance therapy in newly diagnosed disease is uncertain.

METHODS
We conducted an international, randomized, double-blind, phase 5 trial to evaluate the efficacy of olaparib as maintenance therapy in patients with newly diagnosed advanced (International Federation of Gynecology and Obstetrics stage III or IV) high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer (or a combination thereof) with a mutation in BRCA1, BRCA2, or both (BRCA1/2) who had a complete or partial clinical response after platinum-based chemotherapy. The patients were randomly assigned, in a 2:1 ratio, to receive olaparib tablets (300 mg twice daily) or placebo. The primary end point was progression-free survival.

RESULTS
Of the 391 patients who underwent randomization, 260 were assigned to receive olaparib and 131 to receive placebo. A total of 34 patients had a centrally confirmed germline BRCA1/2 mutation, and 2 patients had a centrally confirmed somatic BRCA1/2 mutation. After a median follow-up of 41 months, the risk of disease progression or death was 70% lower with olaparib than with placebo (Kaplan–Meier estimate of the rate of freedom from disease progression and from death at 3 years, 60% vs. 27%; hazard ratio for disease progression or death, 0.30; 95% confidence interval, 0.23 to 0.41; P=0.001). Adverse events were consistent with the known toxic effects of olaparib.
New paradigms for BRCA1/BRCA2 testing in women with ovarian cancer: results of the Genetic Testing in Epithelial Ovarian Cancer (GTEOC) study

Inga Plaskocinska, Hannah Shipman, James Drummond, Edward Thompson, Vanessa Buchanan, Barbara Newcombe, Charlotte Hodgkin, Elisa Barter, Paul Ridley, Rita Ng, Suzanne Miller, Adela Dann, Victoria Licence, Hayley Webb, Li Tee Tan, Margaret Daly, Sarah Ayers, Barnaby Rufford, Helena Earl, Christine Parkinson, Timothy Duncan, Mercedes Jimenez-Linan, Gurdeep S Sagoo, Stephen Abbs, Nicholas Hulbert-Williams, Paul Pharoah, Robin Crawford, James D Brenton, Marc Tischkowitz

ABSTRACT

Background Over recent years genetic testing for germline mutations in BRCA1/BRCA2 has become more readily available because of technological advances and reducing costs.

Objective To explore the feasibility and acceptability of offering genetic testing to all women recently diagnosed with epithelial ovarian cancer (EOC).

Methods Between 1 July 2013 and 30 June 2015 women newly diagnosed with EOC were recruited through six sites in East Anglia, UK into the Genetic Testing in Epithelial Ovarian Cancer (GTEOC) study. Eligibility was irrespective of patient age and family history of cancer. The psychosocial arm of the study used self-report, psychometrically validated questionnaires.

Ovarian cancer and testing for these genes is available through the NHS genetic service if the family history is sufficiently strong to instigate a referral (National Institute for Health and Care Excellence (NICE) guideline CG41). A woman with a mutation in the BRCA1 gene has a 40–60% lifetime risk of developing EOC. For BRCA2 the lifetime risk is lower at 10–30%, but this is still around a 10-fold higher risk than for the general population. At present there is no proven clinical screening for EOC and unaffected women with completed families who carry BRCA1/BRCA2 mutations typically elect to have a prophylactic bilateral salpingo-oophorectomy that reduces the risk of EOC by 80–96%. The prevalence of BRCA1/BRCA2 mutations in the general UK population is estimated to be 1:200. BRCA1/BRCA2 testing is recommended for women with a family history of breast-ovarian cancer, with or without personal history of ovarian cancer, in the context of clinical genetics services.
Referral to Clinical Genetics if EOC <70

Brief pre-test phone consult with Genetic Counsellor

Result given by Genetic Counsellor

If family history form returned ~2 months

BRCA1 and BRCA2 mutation testing criteria

Key: BC: Breast cancer, PC: Prostate cancer, OC: Ovarian cancer, PanC: Pancreatic cancer, MBC: Male breast cancer, FDR: First degree relative

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A woman with breast cancer who...

A woman with ovarian cancer who...

A man with breast cancer who...

1. has OC <70
2. also has BC*
3. has OC >70 and a relative with OC or BC*

*via NHS-GTEOC
Eligible for BRCA1/BRCA2 testing:

‘non-mucinous ovarian cancer at any age’
Mainstreaming testing for germline \textit{BRCA1}/\textit{BRCA2} testing in Epithelial Ovarian Cancer

\textit{BRCA1}/\textit{BRCA2} somatic & germline testing via Gynae-Onc team

Referral to Clinical Genetics if hereditary cause found or strong FHx

Pathway flowchart

Genetic Testing in Epithelial Ovarian Cancer

- Oncologist discusses \textit{BRCA1}/\textit{BRCA2} testing with patient and arranges blood sample (Discussion to include: consent, possibility of VUS, potential need to share information due to possible implications for relatives)

- Oncologist orders \textit{BRCA1}/\textit{BRCA2} testing using EPIC (internal) or paper test request form (external)

- EPIC order/test request form sent directly to Molecular Genetics Laboratory (Cost of testing met by Lab, providing NHS National Genomic Test Directory eligibility criteria are met)

- Result of genetic testing sent directly to clinician who has requested testing (TAT ~8 weeks) Results are NOT sent to Clinical Genetics Clinician may contact genetics with any questions re: result

- Result given to patient by Oncologist/clinician who ordered genetic testing
Figure 1 Genetic counsellor's role in the implementation of genomics.
Supporting Gynae-Oncology teams

**What do patients need to know pre-test?**
May find the cause, other cancer risks
Family implications
Chance of an uncertain variant

**What about the result?**
Language: ‘mutation’ / ‘pathogenic variant’
Keep it simple, having enough time, a clear plan
Refer when mutation found, or strong FHx
Impact on patients

**Positives?**
- Quicker result
- Sooner explanation
- Can guide treatment
- Certainty about other cancer risks
- Improved management
- Access to focussed resources sooner

**Negatives?**
- Less information pre-test?
- Getting result just after diagnosis
- Less time to consider consequences of test?
- Fear of other cancer risks
- Burden of telling family in early treatment
A shift for Genetic Counselling teams

- Educating & supporting non-genetics teams
- Post-test working for families with a hereditary cause
- Aid variant interpretation - context of family history
- Complex cases and longer term family follow up
Example pedigree

Ovarian ca. dx 79

P0022594
BRCA1/BRCA2 no mutations
Ovarian ca. dx 64
Panel testing

Development of NGS
(decrease cost, increase throughput)

Current panel (8 genes)

All with management guidelines

<table>
<thead>
<tr>
<th>ACS, ACOG, ASCO, ClinGen, and/or NCCN Recommendations</th>
<th>Genes (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual screening breast magnetic resonance imaging</td>
<td>ATM, BARD1, BRCA1, BRCA2, CDH1, CHEK2, NBN, NF1, PALB2, PTEN, STK11, TP53</td>
</tr>
<tr>
<td>Earlier and more frequent colonoscopy/endoscopy</td>
<td>APC, AXIN2, BMPR1A, CHEK2, EPCAM, GREM1, MLH1, MSH2, MSH6, PMS2, MSH3 (homozygote, h.); MUTYH (h.), NTLH1 (h.), POLD1, POLE, PTEN, SMAD4, STK11, TP53</td>
</tr>
<tr>
<td>Risk-reducing mastectomy</td>
<td>BRCA1, BRCA2, PALB2, PTEN, STK11, TP53</td>
</tr>
<tr>
<td>Risk-reducing salpingo-oophorectomy, +/- hysterectomy</td>
<td>BRCA1, BRCA2, BRIP1, EPCAM, MLH1, MSH2, MSH6, PMS2, RAD51C, RAD51D</td>
</tr>
<tr>
<td>Risk-reducing colectomy</td>
<td>APC</td>
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<tr>
<td>Risk-reducing gastrectomy</td>
<td>CDH1</td>
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<tr>
<td>Other targeted screening (e.g., RCC, pheochromocytoma)</td>
<td>MEN1, NF2, RB1, RET, SDHAF2, SDHB, SDHC, SDHD, TSC1/2, VHL, TP53, WT1</td>
</tr>
</tbody>
</table>

Table 1: Agreed panels

<table>
<thead>
<tr>
<th>Breast cancer</th>
<th>Ovarian cancer</th>
<th>Colorectal cancer/polyposis</th>
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<tbody>
<tr>
<td>ATM*</td>
<td>BRCA1</td>
<td>APC</td>
</tr>
<tr>
<td>BRCA1</td>
<td>BRCA2</td>
<td>BMPR1A</td>
</tr>
<tr>
<td>BRCA2</td>
<td>BRIP1</td>
<td>EPCAM (del exons 8–9)</td>
</tr>
<tr>
<td>CHEK2†</td>
<td>MLH1</td>
<td>GREM1 (upstream dup)†</td>
</tr>
<tr>
<td>PALB2</td>
<td>MSH2</td>
<td>MLH1</td>
</tr>
<tr>
<td>PTEN</td>
<td>MSH6</td>
<td>MSH2</td>
</tr>
<tr>
<td>STK11</td>
<td>RAD51C</td>
<td>MSH6</td>
</tr>
<tr>
<td>TP53</td>
<td>RAD51D</td>
<td>MUTYH</td>
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<tr>
<td></td>
<td></td>
<td>NTILH1 ‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PMS2</td>
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</table>
BOADICEA V
Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm
Welcome

CanRisk Tool

- Load
- Save
- Reset
- Preferences

- indicates completed stages
- indicates mandatory field
- indicates hover information

Input the information in any order by clicking on the blue bars. Please add as much information as possible. When a section is completed the bar will turn green. If some information is unknown, the bar will not turn green; this does not prevent risk calculation.

Personal Details

Are you? 🏃
Female

In which country do you currently live?
UK
Example pedigree: BRIP1

Likely cause found
BRIP1
$c.2255\_2256\text{delAA}$

P0022594
BRCA1/BRCA2 no mutations
Ovarian ca. dx 64

Predictive testing available

Bilateral salpingo-oophorectomy
age 56

Ovarian ca. dx 79
What about SNPs in Ovarian Cancer risk prediction?
The changing paradigm of diagnostic testing for germline mutations in cancer genetics

Strong FHx
Clear ascertainment
Targeted testing
Genotype correlates with Phenotype
High penetrance

Incidental Finding
Panels, Exomes, Tumour Sequencing
Weak/unknown correlation with phenotype
Lower Penetrance?
Clinical implications less clear
Somatic variants in cancer patients – ‘could this be germline?’

ESMO recommendations for genes to be included for germline-focussed analysis and triggering of germline sample laboratory confirmation

<table>
<thead>
<tr>
<th>Tumour arising any age</th>
<th>Any tumour type</th>
<th>Associated tumour type only</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>• BRCA1</td>
<td>• RAD51C</td>
</tr>
<tr>
<td></td>
<td>• BRCA2</td>
<td>• RAD51D</td>
</tr>
<tr>
<td></td>
<td>• BRIP1</td>
<td>• RET</td>
</tr>
<tr>
<td></td>
<td>• MLH1</td>
<td>• SDHA</td>
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<tr>
<td></td>
<td>• MSH2</td>
<td>• SDHAF2</td>
</tr>
<tr>
<td></td>
<td>• MSH6</td>
<td>• SDHB</td>
</tr>
<tr>
<td></td>
<td>• PALB2</td>
<td>• SDHC</td>
</tr>
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<td></td>
<td>• PMS2</td>
<td>• SDHD</td>
</tr>
<tr>
<td></td>
<td>• VHL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>• TSC2</td>
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<td></td>
<td>• MUTYH&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>• FLCN</td>
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<td>• FH</td>
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<td></td>
<td></td>
<td>• BAP1</td>
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<td></td>
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<td>• POLE</td>
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<table>
<thead>
<tr>
<th>Tumour arising age &lt;30 only</th>
<th>Any tumour type</th>
<th>Associated tumour type only</th>
</tr>
</thead>
<tbody>
<tr>
<td>• RB1</td>
<td>• TP53&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>• APC</td>
<td>• NF1</td>
<td></td>
</tr>
</tbody>
</table>

The future

**Short-term**
Patients entering their family history info securely online

**Medium-term**
Broader panels via mainstreamed testing
SNPs in ovarian cancer risk prediction
Co-ordinated paired tumour/germline sequencing for all

**Longer-term?**
WGS as a default test e.g. done at birth and then selectively interrogated throughout life?
With thanks to

Colleagues in Clinical Genetics
Dr Marc Tischkowitz
Dr Ruth Armstrong
The Genetic Counsellor team
The Clinical Scientist team

Gynae-oncology teams in East Anglia
Patients and their families