Routine *BRCA* testing for Ovarian Cancer Patients

Angela George
Consultant in Oncogenetics
Aims

• Background

• Mainstreaming programme

• Panel testing?

• Beyond ovarian cancer
Demand for genetic testing
Angelina Jolie has double mastectomy due to cancer gene
Traditional genetics model

Referrals for BRCA testing

- Oncologists
- GP / Family Physician
- Surgeons
- Family history clinics
OC patients historically under-referred

- 10% in RMH audit
- 12% in MD Anderson audit\(^1\)
- 20% in Canadian audit\(^2\) (where all eligible for testing)

Why?

1. Failure to take family history
2. Failure to recognise family history
3. Failure to refer (other priorities such as chemo)

\(^1\) Meyer et al Obstet Gynecol 2012
\(^2\) Metcalfe et al, Int J Gynecol Oncol 2009
Referrals and family history

• Cohort study in 3 gynae cancer centres in UK
  – 114 patients had notes examined, from presentation to 2 years after treatment completion
  – Assessed:
    • If family history recorded
    • If appropriate action taken

Lanceley et al; Int J Gynecol Ca, 2012
Results

114 patients

14 had no family history documented

100 patients

15 had insufficient family history recorded to assess

85 patients

22 had sufficient family history to refer to genetics

22 patients

15 were not referred

7 patients

Lanceley et al; Int J Gynecol Ca, 2012
Oncogenetic pathway

- Integration of testing into oncology care
- Educate oncology clinicians to consent patients for testing
  - Including oncologists, specialist nurses
- Testing of patients who meet pre-agreed criteria
- Reduces need to refer to Genetics
Scottish model

• Gynae Medical Oncologists offer testing for BRCA mutations\(^1\)
  – High grade serous ovarian cancer patients initially

• Results returned by oncology team

• Mutation carriers and their families followed up by Clinical Genetics

\(^1\) SIGN Guideline 75
Royal Marsden Model

• Integrated genetic testing into oncology clinics
• Clinicians undergo training to become an ‘approved clinician’
  – Allowed to consent patients and request testing
• Web-based education using 4 short videos
  – www.mcgprogramme.com
• Timing of testing at discretion of individual
Who to test?

• NICE guideline suggested 20% threshold
  – Reduced to 10% in June 2013

• Use of scoring systems, computer programmes
  – Manchester score
  – BOADICEA, BRCAPro

Familial breast cancer
Classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer

Issued: June 2013

NICE clinical guideline 164
guidance.nice.org.uk/cg164
## Manchester score

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Age at Diagnosis</th>
<th>Score</th>
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<tbody>
<tr>
<td>Female breast cancer</td>
<td>&lt;30 years</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>30-39 years</td>
<td>8</td>
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<tr>
<td></td>
<td>40-49 years</td>
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<td>50-59 years</td>
<td>4</td>
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<tr>
<td></td>
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<td>2</td>
</tr>
<tr>
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<td>&lt;60 years</td>
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</tr>
<tr>
<td></td>
<td>&gt;59 years</td>
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<td>13</td>
</tr>
<tr>
<td></td>
<td>&gt;59 years</td>
<td>10</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>Any age</td>
<td>1</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>&lt;60 years</td>
<td>2</td>
</tr>
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</table>
But …

• Up to 50% of ovarian cancer patients with a BRCA mutation have no relevant family history
  – Alsop et al, JCO 2012
  – Moller et al 2007

• (assuming we remember to ask …)
Surrogate endpoints - histology

• High grade serous ovarian cancer
  – 10-20% depending on series

• Endometroid ovarian cancer
  – 8-14%, mostly 10-12%

• Clear cell, undifferentiated, mixed histology
  – 5-15%
• Mucinous
  – ~3%

• Carcinosarcoma
  – Case reports; mostly in carcinoma predominant

• Low grade serous
  – Case reports
Other markers

• Age at diagnosis
  – ? Mean of 50 years for BRCA1, 55 years for BRCA2
  – 60 years for non-BRCA
    • But many confounding features

• Visceral mets (BRCAness?)

• Response to platinum?
Ovarian Pathway

*NHS RMH patient with:
- HG serous or endometroid OC
- <65 yrs at diagnosis

*ACTIONS by approved clinician
1. Information sheet (MS IS1) given to patient
2. BRCA testing discussed
3. Consent obtained and scanned onto EPR
4. Blood (2xEDTA) and request form sent to lab
5. EPR notification to Genetics

*Genetics will issue results. Report and notification to clinician by EPR within 8 weeks.

*MUTATION
Clinician gives result to patient, genetic appt letter sent

*NO MUTATION
Clinician gives result and info sheet (MS IS2) to patient.

More discussion required
Refer to Genetics
### BRCA GENE TEST REQUEST FORM

#### PATIENT DETAILS
- **FIRST NAME(S):**
  - SURNAME: 
  - RMH HOSPITAL NUMBER: 
  - DATE OF BIRTH: 
  - GENDER: 
    - NHS: 
    - PRIVATE: 
  - NHS NUMBER: 
  - POSTCODE: 

#### REASON FOR TEST
- **Cancer Type:**
  - □ Breast
  - □ Ovarian
  - □ Other (please specify) ...........................................

- **Criteria Met for Testing:**
  1. □ Bilateral BC, both cancers <50yrs
  2. □ Triple negative BC <50 yrs
  3. □ Personal history of BC and OC
  4. □ Non-mucinous OC
  5. □ OC and another primary cancer
  6. □ Other (PP only). Please specify ..................................

#### REQUESTING CLINICIAN:
- **Name:** .................................................................
- **Tel:** .................................................................
  (Contact details above required in case of sample query. Results will be returned to Requesting Consultant)

#### REQUESTING CONSULTANT:
- **Name:** .................................................................
- **Hospital / Unit:** .....................................................

#### SAMPLE COLLECTION
- □ Blood : EDTA tubes ONLY (2x 9ml) Sample taken by: ...........................................

- **Date:** .................................................................
  **Time:** .................................................................
  **PLEASE ENSURE NAME AND AT LEAST ONE OTHER IDENTIFIER IS ON TUBE**

#### FOR LABORATORY USE ONLY
- **TGL FAMILY NUMBER:**
- **TGL LAB BARCODE:**

- **LOGGED IN BY:** .................................................................
- **DATE RECEIVED:** .................................................................
  **TIME RECEIVED:** .................................................................

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**PLEASE NOTE:** On receipt of this sample, the laboratory staff assume the appropriate consent has been obtained.
BRCA1 & BRCA2 GENETIC TEST DETAILED REPORT

Referrer details

Requesting clinician: Nazeen Rahman
Consultant: Nazeen Rahman
Department: Gynaecology Unit
Hospital name: RMH
Sample Type: blood

Patient ID

Hospital ID: 
Patient NHS ID: 
TGL sample ID: 
Sample taken: 24/03/2014
Sample received: 24/03/2014 12:48

Referral reason: Ovarian cancer, age at diagnosis: <65
Test: BRCA1 and BRCA2 full gene analysis by Sanger sequencing and MLPA of blood-derived DNA

Patient name: [Blank]  DOB: [Blank]

Result:

<table>
<thead>
<tr>
<th>PATHOGENIC MUTATION DETECTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
</tr>
<tr>
<td>BRCA2 c.3975_3978dupTGCT</td>
</tr>
</tbody>
</table>

Clinical implications:

- The result provides an explanation for why this individual developed cancer.
- Review of result by clinician(s) is recommended to determine implications for clinical management of patient.
- Further information about the cancer risks is available at www.icr.ac.uk/protocols
- Review of patient by Genetics is recommended to discuss implications of this result for themselves and relatives.
- Testing for this mutation can be offered to relatives, through a Genetics department.

Rare variants:

<table>
<thead>
<tr>
<th>None detected</th>
</tr>
</thead>
</table>
CANCER PREDISPOSITION GENE TEST REPORT

Requesting clinician: Joao Lima
Consultant: Susana Banerjee
Department: Gynaecology Unit
Hospital name: RMH
Sample Type: blood

Hospital ID: 
Patient NHS ID: 
TGL sample ID: 14_000308
Sample taken: 02/05/2014
Sample received: 02/05/2014 16:09

Referral reason: Ovarian cancer, age at diagnosis: <65
Test: BRCA1 and BRCA2 full gene analysis using the Illumina TruSight Cancer panel on blood-derived DNA

Patient name: 
DOB: 

BRCA1 and BRCA2 Gene Test Results:

BRCA1: No pathogenic mutation detected
BRCA2: No pathogenic mutation detected

Clinical implications:
• This individual is highly unlikely to have a pathogenic mutation in BRCA1 or BRCA2.
• Review of result by clinician(s) to determine implications for clinical management of patient is recommended.
• Further evaluation in Genetics should be considered for any patient diagnosed with cancer at unusually young age, if there are additional clinical features or if there is a strong family history of cancer.
After 6 months

• 119 patients tested
  – Mutation rate 17%
  – Almost all serous patients
  – Newly diagnosed/relapsed/long-term follow up

• Expanded criteria
Patient with non-mucinous ovarian cancer

*ACTIONS by approved cancer team member
1. Information sheet (MS IS1) given to patient
2. BRCA testing discussed
3. Consent obtained and scanned onto EPR*
4. Blood (2xEDTA) and request form sent to lab

Result reviewed and interpreted by Genetics team

NO MUTATION

Actions by Genetics:
1. Result and information sheet sent to patient
2. Result sent to Cancer team

MUTATION

Actions by Genetics:
1. Result and information sheet sent to patient
2. Result sent to Cancer team

VARIANT REQUIRING EVALUATION (VRE)

Actions by Genetics:
1. Result and information sheet sent to patient
2. Result sent to Cancer team
3. Genetics appt sent to patient

*EPR = electronic patient record
# Demographic Details

<table>
<thead>
<tr>
<th>Category</th>
<th>No Mutation</th>
<th>BRCA1 Mutation</th>
<th>BRCA2 Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>Mean (range)</td>
<td>55.3 yrs (22-79)</td>
<td>50.1 yrs (27-76)</td>
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<tr>
<td></td>
<td></td>
<td>53.6 yrs (44-87)</td>
<td></td>
</tr>
<tr>
<td>Histological Subtype</td>
<td>Serous</td>
<td>138</td>
<td>16</td>
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<tr>
<td></td>
<td>Endometroid</td>
<td>19</td>
<td>0</td>
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<tr>
<td>Stage</td>
<td>I</td>
<td>22</td>
<td>0</td>
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<tr>
<td></td>
<td>IV</td>
<td>30</td>
<td>2</td>
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<tr>
<td>Time of Testing</td>
<td>First Line</td>
<td>52</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Relapse</td>
<td>58</td>
<td>6</td>
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<tr>
<td></td>
<td>Prevalent</td>
<td>50</td>
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<tr>
<td>Relevant Family History</td>
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<td>18</td>
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<td></td>
<td>No</td>
<td>142</td>
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<td>Met Genetics referral criteria</td>
<td>Yes</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>139</td>
<td>8</td>
</tr>
</tbody>
</table>
Evaluation

• All patients happy to have testing in genetics
• No patient would have preferred Genetics input first
• All understood:
  • Testing had implications for them and their family
  • Why they were offered testing
• All clinicians felt testing was important for treatment, and were pleased to be able to offer testing
Family B

[Family tree diagram with specific marking for individual OC 55]
BRCA2 mutation

[Family tree diagram showing individuals with and without BRCA2 mutations, OC 55 (BRCA2 positive), ER+ve BC 52 (BRCA2 negative), and BRCA2 negative]
Dad’s family ...
Dad’s family ...
BRCA2 mutation

- TNBC 82
- OG 55
  - BRCA2
  - BRCA2
- ER+ve BC 52
  - BRCA2
- BRCA2 negative
Benefits of mainstreaming

• Pre-existing relationship with patient
• Testing turnaround time much faster
• Can discuss potential treatment implications with patients
• Negates need for referral to another team and additional hospital visits for patients
• Lower cost for testing
Other genes?

• Lynch syndrome
  – *MLH1, MSH2 (MSH6, PMS2)*
  – ~1% of ovarian cancer patients

• Other homologous repair genes
  – *RAD51C, RAD51D, BRIP1*
  – ~1% combined
  – ? Similar behaviour to *BRCA1* and *BRCA2*
Panel testing?
Pros

• Rapid, comprehensive genetic information
  – Cheaper than sequential, single-gene testing

  – BUT

• How to interpret a previously unseen variant in a little known gene?
Reported Variants

- **BRCA1**
- **BRCA2**
- **MLH1/MSH2/MSH6**
- **PMS2**
- **RAD51C, RAD51D, BRIP1**
Beyond ovarian
### POLO BRCA TEST REQUEST FORM

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<th>PATIENT DETAILS</th>
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<tbody>
<tr>
<td>FIRST NAME(S):</td>
</tr>
<tr>
<td>SURNAME:</td>
</tr>
<tr>
<td>RMH HOSPITAL NUMBER:</td>
</tr>
<tr>
<td>DATE OF BIRTH:</td>
</tr>
<tr>
<td>GENDER:</td>
</tr>
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<td>NHS:</td>
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<tr>
<th>REASON FOR TEST</th>
</tr>
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<tbody>
<tr>
<td>Cancer Type:</td>
</tr>
<tr>
<td>☐ Pancreatic</td>
</tr>
<tr>
<td>Criteria Met for Testing:</td>
</tr>
<tr>
<td>☐ Pancreatic adenocarcinoma, responding/stable after completing platinum-based chemotherapy</td>
</tr>
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<table>
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<th>GENETICS CONSULTANT:</th>
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<tr>
<td>Name: Angela George</td>
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Sample taken by: ____________________________

Date: ____________________________  Time: ____________________________

Please ensure name and at least one other identifier is on tube

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Summary

• *BRCA* testing demand requires alternative testing to traditional method

• An integrated oncogenetic model offers rapid, cost-effective equitable testing

• Other genes likely to become important very soon, further increasing demand
Acknowledgments

- Prof Nazneen Rahman
- Danny Riddell
- Shazia Mahamdallie
- Ann Strydom
- + many others

- www.mcgprogramme.com