Mainstreaming Genetics – what does it mean for breast cancer?

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SouthWest Thames Regional Genetics Service
Overview

• Hereditary breast cancer
• Assessment of genetic predisposition to cancer
• Testing for breast cancer predisposition genes
• Mainstreaming genetic testing
• Somatic v germline mutations
• National Genomic Medicine Service
Hereditary cancer is rare
High risk cancer predisposition genes are rare and dependent on cancer

- Breast cancer: 5-10%
- Colon: 5-10%
- Prostate: 5-10%
- Ovarian: 10-15%
- Melanoma: 10%
- Pancreatic: 10%
- Medullary thyroid: 25%
- Retinoblastoma: 40%
Breast cancer predisposition

- **Sporadic**: 65%
- **High risk genes**: 10%
- **Familial cancer**: 25%
BRCA2
TP53
PTEN
STK11
ATM
CHEK2
~ 180 common variants
BRCA1
PALB2
CDH1
Risk for gene carriers vs polygenic risk

Risk of breast cancer (%) vs Age

- BRCA1
- BRCA2
- Polygenic risk
- General Population
How can we identify patients with high risk cancer predisposition genes?

- Family history
- Pathology of cancer
- High risk CPG
- Syndromic features
- Tumour testing
1) An individual with breast cancer (BC):
   - 1) Was diagnosed <30 (offer tp53 testing/100K if negative result)
   - 2) Has bilateral BC and both cancers diagnosed <50 years
   - 3) Has triple negative BC diagnosed < 60 years, or ER-/ve and PR/HER2 status unknown <40
   - 4) Also has OC
   - 5) Has bilateral BC and a relative with BC <60 (can test either pt)
   - 6) Has a relative with BC and both diagnosed <45
   - 7) <40 years old + no information on biological relatives (adopted)
   - 8) Has relatives with cancer with Manchester score ≥ 15
   - 9) Was diagnosed <50 and has Jewish or Polish ancestry*
   - 10) Has relatives with cancer with Manchester score ≥ 10 and has Jewish or Polish ancestry*  *Founder mutation screen only

2) An individual with ovarian cancer (OC) or uterine serous cancer:
   - 1) Where histology confirms non-mucinous ovarian cancer
   - 2) All uterine serous cancers

3) An individual with pancreatic cancer or prostate cancer:
   - 2) Has relatives with cancer with Manchester score ≥ 15.
     If affected relative with breast or ovarian cancer available to test should offer testing to this individual first.

4) An individual unaffected with cancer:
   - 1) Has relatives with cancer with Manchester score ≥ 17 where tumour blocks containing normal tissue are available from an affected FDR with OC or BC <50 to be sent for BRCA test
   - 2) Has relatives with cancer with Manchester score ≥ 17, one must be FDR and no affected relatives available to test.
   - 3) Has Jewish or Polish ancestry and a FDR relative with BC <50 or OC or relatives with cancer with Manchester score ≥ 10, one must be FDR, and no affected relatives available to test*

   BC<40 / OC / FDR diagnosis must be confirmed.
   *Founder mutation screen only

**MANCHESTER SCORE**

<table>
<thead>
<tr>
<th>CANCER, AGE AT DIAGNOSIS</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female BC, &lt;30</td>
<td>11</td>
</tr>
<tr>
<td>Female BC, 30-39</td>
<td>8</td>
</tr>
<tr>
<td>Female BC, 40-49</td>
<td>6</td>
</tr>
<tr>
<td>Female BC, 50-59</td>
<td>4</td>
</tr>
<tr>
<td>Female BC, &gt;59</td>
<td>2</td>
</tr>
<tr>
<td>Triple negative BC</td>
<td>4</td>
</tr>
<tr>
<td>Male BC &lt;60</td>
<td>13</td>
</tr>
<tr>
<td>Male BC, &gt;59</td>
<td>10</td>
</tr>
<tr>
<td>OC, &lt;60</td>
<td>13</td>
</tr>
<tr>
<td>OC, &gt;59</td>
<td>10</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>1</td>
</tr>
<tr>
<td>Prostate cancer, &lt;60</td>
<td>2</td>
</tr>
<tr>
<td>Prostate cancer, &gt;59</td>
<td>1</td>
</tr>
</tbody>
</table>

1 intervening female relative allowed.
2 intervening females allowed if one died or had RRS <50 years.

BC = Breast cancer  FDR = First degree relative
OC = Ovarian cancer  RRS = Risk reducing surgery

Ipsilateral breast cancers occurring ≥ 5 years apart count as bilateral. DCIS/LCIS count as invasive cancer.
Female relatives through intervening male relative count as closer degree of relative.

20/07/2017
Diagnostic versus predictive testing

- Diagnostic test (full screen) is undertaken in someone with disease i.e. cancer.
- Predictive test (targeted test) is undertaken in an unaffected individual where familial mutation is already known
<table>
<thead>
<tr>
<th>Outcomes of genetic testing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathogenic variant identified</strong></td>
</tr>
<tr>
<td>- Clinically actionable – manage as per high risk gene</td>
</tr>
<tr>
<td>- Cascade screening (predictive testing) for family</td>
</tr>
<tr>
<td><strong>No variant identified – normal result</strong></td>
</tr>
<tr>
<td>- Manage on family history</td>
</tr>
<tr>
<td><strong>Variant of uncertain significance (VUS) identified</strong></td>
</tr>
<tr>
<td>- Analyse variant in MDT with clinical scientists</td>
</tr>
<tr>
<td>- Normally not clinically actionable</td>
</tr>
<tr>
<td>- In majority of cases, manage on family history</td>
</tr>
<tr>
<td><strong>Benign variant identified – normal result</strong></td>
</tr>
<tr>
<td>- Manage on family history</td>
</tr>
</tbody>
</table>
breast cancer 38 yrs

breast cancer 54 yrs

ovarian cancer 64 yrs

breast cancer 37 yrs

ovarian cancer 57 yrs

BRCA2
breast cancer 38 yrs

ovarian cancer 64 yrs  breast cancer 54 yrs

breast cancer 37 yrs

ovarian cancer 57 yrs
What is mainstreaming?

• Genetic testing of cancer predisposition genes (CPG) has been traditionally undertaken by Clinical Genetics
  – Traditionally low through put
  – Arose primarily to serve unaffected family members
Identifying patients with high risk CPG has high clinical utility

Patient with cancer

- Informs medical management and surgical options
- Provides reason for why developed cancer
- Informs patient about future cancer risk
- Informs relatives about their cancer risk—access to screening and risk reducing surgery
What is mainstreaming?

- Genomics revolution: better technologies, increased testing, increased utility to patients
Genetic testing

- Single gene
- NGS panel
- WES
- WGS
What is mainstreaming?

• Genomics revolution: better technologies, increased testing, increased utility to patients
• Strong rationale for increased genetic testing of CPG
• Need to upscale current testing
• Mainstreaming = specialties other than genetics undertaking genetic testing (Oncology, Cardiology, Neurology etc)
How successful has mainstreaming been so far?

• RMH implemented highly successful Oncogenetic mainstreaming model through MCG programme
• Testing of *BRCA1* and *BRCA2* undertaken by Breast and Gynae Teams following training
• Test results interpreted and returned by letter to patient by Genetics
• Positive patient and clinician feedback
Eligible Cancer Patient

**Actions by approved clinician**
1. Information sheet (MS IS1) given to patient.
2. BRCA testing discussed.
3. Consent obtained.
4. Blood and request form sent to lab.

More discussion required

Refer to Genetics

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**NO MUTATION**

Actions by Genetics:
1. Result and information sheet (MCG IS2) sent to patient.
2. Result sent to Cancer Team.

**MUTATION**

Actions by Genetics:
1. Result and information sheet (MCG IS3) sent to patient.
2. Result sent to Cancer Team.
3. Genetics appt sent to patient.

**VARIANT REQUIRING EVALUATION (VRE)**

Actions by Genetics:
1. Send result and information sheet (MCG IS4) to patient.
2. Result sent to Cancer Team.
3. Genetics appt sent to patient.
Other centres

• Many centres have implemented a mainstreaming programme for ovarian cancer
• Test criteria for ovarian is straightforward
  – All women with non-mucinous ovarian cancer
• Testing criteria for breast cancer more complex
  – Dependent on personal history and family history
Barriers to mainstreaming

• Funding difficult
  – Genetics activity and test cost coupled
  – Other specialties -no budget for genetic testing

• Adhere to 10% mutation detection –often requires assessment of family history, complex criteria

• Regional Genetics Centre cover many Oncology centres -training and education
Other models

• Rapid pathways
  – Oncology take blood sample and have short discussion with patient
  – Genetic undertake telephone consultation

• Embedded model
  – Genetics Counsellor attends Oncology clinic
Affected with breast or ovarian cancer and BRCA result will affect surgical or medical treatment *
*BRCA result will result in a change in chemotherapy from standard protocol or result in different surgical decision

Box A.
- Breast cancer under 30 years
- Triple negative breast cancer under 60 years
- Bilateral breast cancer under 50 years
- Breast cancer under 45 years and another relative** also affected under 45 years
- Breast cancer and ovarian cancer any age
- Non-mucinous ovarian cancer any age
**sister/mother/grandmother/aunt on maternal or paternal side

Box B. Does not meet Box A criteria, but at least two relatives affected with breast cancer or one relative with male breast cancer or ovarian cancer

Patient meets criteria for rapid assessment
Please make patient aware that referral is for an assessment and testing may not be offered

1. Take blood sample and consent for test
2. Complete Rapid BRCA referral and blood form
3. Email cancergenetics.stg@nhs.net or call x5335
4. Patient will be contacted by Genetics team within two working days for consultation to assess if eligible for BRCA test
5. If Genetics team determine patient eligible for test, BRCA result will be available within four weeks of blood sample being received in the Genetics lab

National Genomic Medicine Service

• We now have a National Genomic Medicine service!
• National Lab reconfiguration - 24 labs reduced to 7 Genomic Laboratory Hubs (GLH)
• Creation of National Genetic Test Directory
• Aims to standardise the tests available throughout England
• Range from single gene testing to whole genome sequencing
Cancer = Two genomes

Constitutional/germline

Management of future cancer risks and relative’s cancer risks

Clinical management of current cancer/relapse

Somatic
Cancer = Two genomes

Management of future cancer risks and relative’s cancer risks

Clinical management of current cancer/relapse

Constitutional/germline

Somatic

Rare disease test directory

Cancer test directory
National Test Directory -cancer

- Panel testing of actionable mutations
- WGS for childhood cancer, sarcoma and hematological (paired tumour and germline)
<table>
<thead>
<tr>
<th>Condition</th>
<th>Panel Description</th>
<th>Detection Method</th>
<th>Pathology/Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer (somatic)</td>
<td>Multi-target NGS panel - small variant (BRCA1, BRCA2)</td>
<td>Small variant detection</td>
<td>Known high grade serous ovarian carcinoma</td>
</tr>
<tr>
<td></td>
<td>Multi-target NGS panel - small variant (SMARCA4)</td>
<td>Small variant detection</td>
<td>In cases of diagnostic uncertainty of small cell carcinoma of the ovary</td>
</tr>
<tr>
<td>Solid Tumour (Adult)</td>
<td>Oncotype DX</td>
<td>Multiple</td>
<td>As per NICE recommendations in ER positive, HER2 negative, lymph node negative early breast cancer</td>
</tr>
<tr>
<td>Core Ovarian Carcinoma</td>
<td>Endopredict</td>
<td>Multiple</td>
<td>As per NICE recommendations in ER positive, HER2 negative, lymph node negative early breast cancer</td>
</tr>
<tr>
<td>Core Breast Cancer</td>
<td>Prosignia</td>
<td>Multiple</td>
<td>As per NICE recommendations in ER positive, HER2 negative, lymph node negative early breast cancer</td>
</tr>
</tbody>
</table>
National Test Directory – rare disease (hereditary cancer)

• Multiple testing indications
• Single gene and small panels
• R207 and R208 – breast and ovarian

https://www.england.nhs.uk/publication/national-genomic-test-directories/
R208 Inherited breast cancer and ovarian cancer

Testing Criteria

1. Living affected individual (proband) with breast or ovarian cancer where the individual +/- family history meets one of the criteria. The proband has:
   a. Breast cancer (age < 30 years), OR
   b. Bilateral breast cancer (age < 50 years, OR
   c. Triple negative breast cancer (age < 60 years), OR
   d. Male breast cancer (any age), OR
   e. Non mucinous ovarian cancer at any age, OR
   f. Breast cancer (age < 45 years) and a first degree relative with breast cancer (age < 45 years), OR
   g. Pathology-adjusted Manchester score ≥15 or BOADICEA score ≥10%
   h. Ashkenazi Jewish ancestry and breast cancer at any age

2. Deceased affected individual with breast or ovarian cancer with:
   a. A stored DNA, blood or tissue sample available for DNA extraction, AND
   b. Pathology-adjusted Manchester score ≥17 or BOADICEA score ≥15%, AND
   c. No living affected individual is available for genetic testing

3. Living unaffected individual with:
   a. first degree relative affected by breast or serous ovarian cancer, AND
   b. Pathology-adjusted Manchester score ≥20 or BOADICEA score ≥20% (for the first degree relative), AND
   c. No living affected individual is available for genetic testing, AND
   d. No deceased affected individual with tumour material available for testing

BRCA1, BRCA2 and PALB2 (TP53 <30 yrs or other syndromic genes where clinical features)
Ordering Tests

• Tests will be ordered online through a centralised web portal
• Who can order tests will be specified
• Many inherited cancer gene tests will be “mainstreamed” – can be requested by Oncologists/Surgeons
• Implementation - ?July/October 2019
How will this alter pathways?

• Genetic testing can be mainstreamed
• Overcomes funding issues
• National consistency
How will this alter pathways?

• If testing undertaken in Oncology
  – Full consent will need to be undertaken by Oncology
  – Results will be returned to Oncology
  – Patients with pathogenic mutation will need to be referred to Genetics
  – Patients with variants of uncertain significance will need to be referred to Genetics
  – Family members will need to be seen by genetics for predictive testing
  – Patients with family history will still require evaluation of family history to determine screening requirements
Breast surveillance guidelines for women with family history of breast cancer and no familial mutation

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### Protocol 1

**Management guidelines for unaffected women with a family history of breast and/or ovarian cancer**

<table>
<thead>
<tr>
<th>Category B1 surveillance</th>
<th>Category B2 surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual mammography 40-50 years</td>
<td>Annual mammography 40-60 years</td>
</tr>
<tr>
<td>Three-yearly mammography 50-70 years</td>
<td>Three-yearly mammography 60-70 years</td>
</tr>
</tbody>
</table>

#### Key
- FDR = First degree relative
- MDR = Second degree relative
- TDR = Third degree relative
- BC = Breast Cancer
- OC = Ovarian Cancer

#### 1 relative with breast cancer
- One female FDR with BC at < 40 yrs
- One male FDR with BC at any age
- One FDR with bilateral BC at any age

#### 1 relative with breast and ovarian cancer
- One FDR with BC and OC at any age

#### 2 relatives with breast cancer
- Two female FDR with BC at any age
- One female FDR and one female SDR with BC at any age
  - Bilateral BC, any age and another relative < 60 yrs, pt least one must be FDR
  - Both cancers < 50 yrs

#### 2 relatives: one with breast and one with ovarian cancer
- One OC and one BC at any age
  - pt least one must be FDR

#### 2 or more relatives with ovarian cancer
- Three female FDR or SDR with BC at any age
  - Two are FDR or Two are MDR and one is FDR or FDR or FDR < 55 yrs

#### 3 relatives with breast cancer
- Three FDR or SDR with BC at any age
  - One FDR with bilateral BC
  - pt least one must be FDR

#### 3 relatives with breast or ovarian cancer
- Three FDR or SDR with BC or OC at any age
  - At least two are OC pt least one must be SDR

#### 4 or more relatives with breast or ovarian cancer
- FDH/OC/BDH with BC or OC at any age

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Notes:
- If the consultee has breast cancer and has residual breast tissue, count as a FDR for surveillance recommendations.
- An affected female SDR through a male FDR is equivalent to a FDR.
- One relative must be a FDR of the consultee, unless otherwise specified.
- Discussion of chemoprevention should include potential benefits and side effects & review of contraindications.

### BRCA negative families
- For breast only families, a negative BRCa test does not alter the mammographic surveillance recommendations.
- One relative must be a FDR of the consultee, unless otherwise specified.
- Surveillance should include potential benefits and side effects & review of contraindications.

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09/02/2015 v1

* See FAQ document for further details [http://www.icr.ac.uk/protocols]
How can assessment of family history be managed if genetic testing mainstreamed?
Consent, Data protection and Data Privacy

Please read the following and click accept if you wish to continue.

Why do we need this data?
Cancer is sadly a common disease. Up to 1 in 2 people will develop cancer in their lifetime. However, some people have an increased chance of developing cancer in their lifetime due to underlying factors in their genetic code. For these people, putting extra screening or prevention measures in place to try to avoid them developing an untreatable cancer can help us decide whether you have an increased chance of developing cancer in your lifetime. We use family history as a guide. We look at the number of people who have developed cancer in your family, the ages the cancers developed, the types of cancer in the family, and how closely related the relatives with cancer are. This information helps us decide whether any genetic testing is needed, or, more commonly, whether any extra screening is needed for you and your relatives.

How will your data be used?
A trained assessor will review your family history data and then either offer you an appointment to speak with a genetic counsellor or geneticist, or send you a letter with a cancer risk assessment and screening advice. The data will be used for the purposes of advising you and your relatives on future cancer risks.

What information about my family will be stored?
The information you have provided will be kept on a secure, confidential NHS database, unless you ask us to remove it. The data is stored so that if your medical history, or your family history changes in the future, we can use this previous data alongside the new data to give you an up to date risk assessment. The secure database is accessed by trained professionals within the clinical genetics department.

How long will your data be kept?
Your data will be held securely on the clinical genetics database indefinitely, but you can request removal of your data at any time.

How can I ask for my data to be removed from the database?
If you do not wish for your data to be stored, you can contact our department by post, telephone or email, and we can remove your personal data after your assessment. You would then need to provide the data again if you required a new assessment.
Output: genetic testing required

Risk Assessment:

Manchester Score - BOADICEA -

Patient is eligible for genetic testing. Please refer to clinical genetics.
Output: screening required

Risk Assessment:
Manchester Score - BOADICEA -

Patient is eligible for annual mammograms between the ages of 40-50 and thereafter three yearly through the NHS breast screening programme. Please refer them to their local screening service.
What should I do?

• Collaboration with Genetics
  – Discuss new pathways – decide on what tests to mainstream
  – Arrange education days/training sessions
  – Ensure all mutation positive are referred to Genetics
  – All mutation positive should be referred to Genetics
  – Family members of patients with normal genetic test result and family history should be referred to genetics/ family hx clinic for screening advice
Future changes

• Likely testing threshold will decrease to 5% or less
• Testing of more breast cancer predisposition genes e.g ATM and CHEK2
• Paired tumour and germline sequencing
Genomic Data

Somatic tumour data
- Genomic tumour advisory board GTAB weekly
- Integrated molecular report
- “Genomics section” Tumour specific MDTs

Germline data
- Cancer genetics clinician weekly cancer genetics MDT
- Clinical genetics report
Summary

• Hereditary breast cancer is rare
• Identification of patients with CPG is important for cancer management and wider family
• Genetic testing will increasingly be undertaken in mainstream specialties
• Genetics role will shift from pre-test to post test
Thank you