Familial Cancer and Genomics

Dr. Jude Hayward

GPwSI in Genetics: Yorkshire and Humber GMC
Primary Care Adviser to HEE Genomics Education Programme
RCGP Joint Clinical Champion for Genomics
GP: Shipley Medical Practice, Affinity Care
Outline

• Familial Cancer (focus on familial breast cancer)
• Risk assessment
• Principles of management
• Genomic testing in familial / cancer
Mrs. B

‘My mother had breast cancer when she was very young – she was only 47’
‘I want the cancer gene test to see if I’ll get breast cancer’
Familial Cancer: Multifactorial inheritance

- Cancer is a condition of multifactorial aetiology: a spectrum where environmental factors dominate at one end, with a gradation of genetic susceptibility towards predominantly genetic factors at the other end.

- Only ~5% of breast cancers occur as a result of an underlying inherited cancer syndrome.

Environmental aetiology

Above-population risk based on epidemiological data: likely contribution of several genes (polygenic) with individually smaller effects: 10-15%

‘High risk’ – single gene condition, autosomal inheritance: 5%

Genetic aetiology

Multifactorial Inheritance
# Inherited Cancer Syndromes

<table>
<thead>
<tr>
<th>Cancer syndrome/ Lifetime risk of cancer for women</th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>HNPCC (Lynch)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>80%</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td>40%</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td>Endometrial</td>
<td></td>
<td></td>
<td>60%</td>
</tr>
<tr>
<td>Male breast cancer</td>
<td>Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic</td>
<td>Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td></td>
<td></td>
<td>60-80%</td>
</tr>
<tr>
<td>Gastric</td>
<td></td>
<td></td>
<td>Y</td>
</tr>
<tr>
<td>GU tract</td>
<td></td>
<td></td>
<td>Y</td>
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</table>
Familial Cancer: red flags?

• Cancers occurring as a result of an inherited cancer syndrome typically present at a younger age, may be bilateral and associated with other malignancies

• Risk assessment: Taking a family history in primary care is key

• Risk stratification either as near-population or above-population risk within primary care is crucial to appropriate management
Assessment in Primary Care

Breast Symptoms

- **NO**
- **YES** → Breast Unit

Known gene mutation in the family, or referral recommended by another Genetics service

- **NO**
- **YES** → Regional Genetics Service / Genomics Medicine Centre

Assess family history
Assessment in Primary Care

Patients may be managed in primary care if they are at near-population risk:

i.e. have one 1st or 2nd degree relative presenting with unilateral breast cancer >40 yrs with no additional factors (see list on the right of slide)

Seek advice from secondary care if needed

- Bilateral breast cancer
- Male breast cancer
- Ovarian cancer
- Jewish ancestry
- Sarcoma <45 years
- Glioma or childhood adrenocortical carcinoma
- Complicated patterns of multiple cancers at a young age
- Paternal history breast cancer (2 or more relatives)
Near-population risk (NICE)

- Return if family history alters
- Breast awareness symptoms
- National screening programmes
- Contact details for support groups
- Lifestyle advice:
  - HRT and contraception
  - Diet, alcohol, smoking etc.
  - Breast feeding, family size etc.
Contraception and HRT

<table>
<thead>
<tr>
<th>UKMEC (2016) Guidance</th>
<th>CHC</th>
<th>PO</th>
<th>IUD/Barrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family History of Breast Cancer</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Carriers of known gene mutations associated with breast ca e.g. BRCA1/2</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

NICE guidance: **Familial Breast Cancer**

- Consider all cancer-associated risk: CHC methods reduce lifetime risk of ovarian cancer

NICE guidance: **Menopause**
[www.nice.org.uk/guidance/ng23/chapter/Recommendations](http://www.nice.org.uk/guidance/ng23/chapter/Recommendations)
‘My mother had breast cancer when she was very young – she was only 47’

‘My sister has been told she has it now too, she is 42’
Above-population risk

Refer to secondary care (breast unit):

• One relative
  • Female 1\textsuperscript{st} degree with breast ca <40
  • Male 1\textsuperscript{st} degree with breast ca at any age
  • Female 1\textsuperscript{st} degree with bilateral breast ca <50
  • 1\textsuperscript{st} degree with breast and ovarian ca

• Two relatives
  • 1\textsuperscript{st}/2\textsuperscript{nd} degree with breast ca at any age
  • 1\textsuperscript{st}/2\textsuperscript{nd} degree with breast and ovarian cancer
  • With breast and/or ovarian cancer on paternal side

• Three relatives:
  • 1\textsuperscript{st} or 2\textsuperscript{nd} degree with breast cancer at any age
Management in secondary care:

Formal lifetime risk assessment (breast cancer)
Advice re surveillance and risk reduction

Moderate risk (17-30%):
- Annual mammogram 40-50
- 18/12 mammogram 50-60
- NHSBSP
- Tamoxifen / Anastrazole

High risk (>30%):
- Annual mammogram 40-60
- NHSBSP
- Tamoxifen / Anastrazole
Management in secondary care

Assess risk of BRCA / other pathogenic variant:

- Those eligible for genetic testing (using Manchester Scoring System):
  - $>10\%$ chance of BRCA mutation

- Any unusual family history
- Jewish Ashkenazi Ancestry
Genetics or genomics?

- **Genetics** is used in discussion of single gene diseases e.g. cystic fibrosis or haemophilia.

- **Genomics** refers to a person’s entire genetic code / DNA - their genome. Variations in different parts of a genome might increase or decrease the chances of developing many common (multifactorial and polygenic) diseases such as diabetes or heart disease.

- **Genomic Medicine** refers to the application of genomics to clinical care of patients; Regional Genetics Centre have now become Genomics Medicine Centres.
Genomics Medicine Centres

- Risk assessment
- Surveillance
- Advised regarding risk-reducing measures
- Consideration for genetic / genomic testing:
  - Single gene testing
  - Testing of multiple genes (gene ‘panels’)
  - Whole genome sequencing: 100,000 Genomes Project
100,000 Genomes Project

The 100,000 Genomes Project

The project will sequence 100,000 genomes from around 70,000 people. Participants are NHS patients with a rare disease, plus their families, and patients with cancer.

The aim is to create a new genomic medicine service for the NHS – transforming the way people are cared for. Patients may be offered a diagnosis where there wasn't one before. In time, there is the potential of new and more effective treatments.
BRCA 1 / 2 pathogenic variant

- Changes risk significantly
- Screening:
  - 30-50: Breast MRI
  - 50 onwards: annual mammogram
- Risk-reducing options:
  - Bilateral mastectomy
  - Bilateral salphingo-oophorectomy
- Implications for family members: risk and predictive testing
Genomic testing: Ovarian Cancer

- 13% of patients diagnosed with ovarian cancer carry a BRCA1/2 pathogenic variant

- Testing now offered in secondary care setting at time of diagnosis
Genomics and targeted cancer treatment

Based on germline testing
- Olaparib is only effective in BRCA1/2 carriers: 3\textsuperscript{rd} line treatment for women with ovarian cancer

Based on somatic testing: genomic testing of a tumour (cf germline testing)
- Her2 testing in breast cancer to predict response to Herceptin
Access to genomic testing is increasing

- Changing criteria for testing within routine clinical care
- Mainstreaming: genomic testing for patients at point of cancer diagnosis within oncology / secondary care
- Genomic testing of cancers for targeted treatment
- Testing of multiple genes simultaneously: gene ‘panels’
- Eligibility for 100,000 Genomes Project
- Increasing availability of commercial testing (Direct-to-consumer testing)
Family history of colorectal cancer

Near-population risk: If 1 relative >50 y.o.a., and no related cancers (endometrial, ovarian, pancreatic, gastric, biliary, GU tract)

Advice: symptom awareness, lifestyle factors, return if family history alters, NHS Bowel screening programme

Otherwise refer:
• Known gene mutation within the family
• 1 relative <50 y.o.a.
• 2 first-degree relatives
• 2 relatives average <60 y.o.a.
• 3 relatives any age
• Unusual cancers as above

BSG/ACPGBI guidelines for colorectal cancer screening and surveillance in moderate and high risk groups
Family history of ovarian cancer

Investigate symptoms (NICE guidelines: *Suspected Ovary Cancer*)

Screening asymptomatic women via Ca125 and USS has NOT proven effective

Review family history / refer to Genomics Medicine Centre if:
- known gene mutation in family or advised by another genetics service
- 2 or more cancers: ovarian and/or associated cancers
- **NB:** 2 ovarian cancer, or 1 ovarian + 1 breast cancer now eligible for BRCA testing
- Associated cancers: colorectal, endometrial, other GI (gastric, small bowel), GU tract
In summary:

- Around 5% cancer results from an inherited cancer syndrome

- Risk assessment: family history
  - Clustering of any cancer in a family is a ‘red flag’
  - e.g. 3 relatives with same cancer >60 yoa, 2 relatives <60 yoa.

- Common management principles: Surveillance, Risk-reduction / lifestyle advice, symptom awareness, review if family history changes

- Genomic testing is advancing knowledge of Familial Cancer and Inherited Cancer Syndromes and advancing targeted treatment for cancer

- Increasing access to genomic testing will impact on primary care
Information for patients

- www.macmillan.org.uk
- www.cancerresearch.org
- www.breastcancercare.org.uk
- www.ovarian.org.uk
- www.breastcancergenetics.co.uk
- www.nhs.uk/conditions/breast-cancer-screening/when-its-offered/
Thank you

- For more information on genomics in primary care, please visit: http://www.rcgp.org.uk/clinical-and-research/our-programmes/innovation/genomics-in-medicine.aspx

- For questions or comments please contact us at genomics@rcgp.org.uk

- For more information on genomics education, please visit: https://www.genomicseducation.hee.nhs.uk/