Genetic counseling and testing

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Disclosures

Roche: Speakers bureau, honoraria, consultancy
Astra Zeneca: Speakers bureau, honoraria, consultancy
Novartis: Speakers bureau, honoraria, consultancy
Pfizer: Speakers bureau, honoraria, consultancy
Cancer Arises From Gene Mutations

**Germline mutations**
- Present in egg or sperm
- Are heritable
- Cause cancer family syndromes

**Somatic mutations**
- Occur in nongermline tissues
- Are nonheritable

Mutation in egg or sperm → All cells affected in offspring → Somatic mutation (e.g., lung)
• Cancer can cluster in families because of shared environmental exposures (diet, lifestyle, “environment”, work related exposures)

• Those 15-20% referred to as “familial”, may be caused by the interaction of low-penetrance genes, gene-environment interaction, or both
**Sporadic cancers**
- Age appropriate
- Common cancers

**Familial Cancer**
- Occurring in or affecting more members of family than would be expected by chance
- Generally, two or more family members with the same type of cancer, age appropriate

**Hereditary cancers**
- Multiple affected family members
- Early onset
- Bilateral BC or multiple primaries
- Clustering in family of diseases suggestive of a hereditary cancer syndrome
- Extensive family history

**Risk for cancer**
- Sporadic cancers: AVERAGE
- Familial Cancer: MODERATE
- Hereditary cancers: HIGH
BRCA1/2 Mutations
BRCA1 and BRCA2

- Cloned in families with multiple cases of breast and/or ovarian cancer

BRCA1- cloned 1994

BRCA2- cloned 1995

Mutations in different genes can cause the same disease.
Prevalence

In unselected populations - \( \frac{1}{300} - \frac{1}{800} \).

**Founder mutations:**

Iceland - BRCA2 999del5 - 0.6\% (~1/170)

Ashkenazi Jews -

BRCA1 - 185del AG 1\%  
5382insC 0.1\%

BRCA2 - 6174delT 1.4\%  
2.5\% (1/40)
The prevalence of BRCA1/BRCA2 mutations: Contribution to cancer

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Non-selected population</th>
<th>Ashkenazi Jewish</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>2.5-5%</td>
<td>~11%</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>10-15%</td>
<td>~40%</td>
</tr>
<tr>
<td>Pancreatic Cancer</td>
<td>?</td>
<td>~8%</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>?</td>
<td>~5%</td>
</tr>
</tbody>
</table>
Cancer susceptibility genes other than BRCA1/2

<table>
<thead>
<tr>
<th>Cancer Susceptibility Gene</th>
<th>Breast Cancer RR (90% CI when available) or Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast</strong></td>
<td></td>
</tr>
<tr>
<td>ATM</td>
<td>2.8 (2.2 to 3.7) (^{35})</td>
</tr>
<tr>
<td>BARD1</td>
<td>Breast cancer association reported; RR not yet determined (^{17,46,47})</td>
</tr>
<tr>
<td>BRIP1</td>
<td>2.0 (1.3 to 3.0) (^{48}); ovarian cancer RR 11.2 (^{9})</td>
</tr>
<tr>
<td>CDH1</td>
<td>6.6 (2.2 to 9.9) (^{49})</td>
</tr>
<tr>
<td>CHEK2</td>
<td>3.0 (2.6 to 3.5) (^{35}); most data for 1100delC</td>
</tr>
<tr>
<td>NBN</td>
<td>2.7 (1.9 to 3.7) (^{35})</td>
</tr>
<tr>
<td>PALB2</td>
<td>5.3 (3.0 to 9.4) (^{35})</td>
</tr>
<tr>
<td>PTEN</td>
<td>RR 2.0-5.0 (^{50,51})</td>
</tr>
<tr>
<td>STK11</td>
<td>RR 2.0-4.0 (^{52,53})</td>
</tr>
<tr>
<td>TP53</td>
<td>105 (62 to 165) (^{35})</td>
</tr>
</tbody>
</table>

Tung et al JCO 2016
When to refer for onco-genetic counseling & testing?
BRCA1/2 TESTING CRITERIA

Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management.

Testing of an individual without a cancer diagnosis should only be considered when an appropriate affected family member is unavailable for testing.

**Individual from a family with a known deleterious BRCA1/BRCA2 gene mutation**
- Personal history of breast cancer \(^b\) + one or more of the following:
  - Diagnosed ≤45 y
  - Diagnosed ≤50 y with:
    - An additional breast cancer primary \(^c\)
    - ≥1 close blood relative \(^d\) with breast cancer at any age
    - ≥1 close blood relative with pancreatic cancer
    - ≥1 relative with prostate cancer (Gleason score ≥7)
    - An unknown or limited family history \(^a\)
  - Diagnosed ≤60 y with:
    - Triple negative breast cancer
    - Diagnosed at any age with:
      - ≥2 close blood relatives with breast cancer, pancreatic cancer, or prostate cancer (Gleason score ≥7) at any age
      - ≥1 close blood relative \(^d\) with breast cancer diagnosed ≤50 y
      - ≥1 close blood relative \(^d\) with ovarian \(^e\) carcinoma
      - A close male blood relative \(^d\) with breast cancer
      - For an individual of ethnicity associated with higher mutation frequency (e.g., Ashkenazi Jewish) no additional family history may be required \(^d\)
    - Personal history of ovarian \(^e\) carcinoma
    - Personal history of male breast cancer

**Personal history of prostate cancer (Gleason score ≥7) at any age with ≥1 close blood relative \(^d\) with ovarian carcinoma at any age or breast cancer ≤50 y or two relatives with breast, pancreatic, or prostate cancer (Gleason score ≥7) at any age**

**Personal history of pancreatic cancer at any age with ≥1 close blood relative \(^d\) with ovarian carcinoma at any age or breast cancer ≤50 y or two relatives with breast, pancreatic cancer, or prostate cancer (Gleason score ≥7) at any age**

**Personal history of pancreatic cancer and Ashkenazi Jewish ancestry**

**BRCA1/2 mutation detected by tumor profiling in the absence of germline mutation analysis**

**Family history only** (significant limitations of interpreting test results for an unaffected individual should be discussed):
- First- or second-degree blood \(^d\) relative meeting any of the above criteria
- Third-degree blood \(^d\) relative who has breast cancer \(^b\) and/or ovarian \(^e\) carcinoma and who has ≥2 close blood relatives \(^d\) with breast cancer (at least one with breast cancer ≤50 y) and/or ovarian \(^e\) carcinoma

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\(^a\)For further details regarding the nuances of genetic counseling and testing, see BR/OVA.

\(^b\)For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.

\(^c\)Two breast cancer primaries includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors either synchronously or asynchronously.

\(^d\)Close blood relatives include first-, second-, and third-degree relatives on same side of family. (See BR/OV-B)

\(^e\)Includes fallopian tube and primary peritoneal cancers. BRCA-related ovarian cancers are associated with epithelial non-mucinous histology. Lynch syndrome can be associated with both nonmucinous and mucinous epithelial tumors. Be attentive for clinical evidence of Lynch syndrome (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal). Specific types of non-epithelial ovarian cancers and tumors can also be associated with other rare syndromes. Examples include an association between sex-cord tumors with annular tubules and Peutz-Jeghers syndrome or Sertoli-Leydig tumors and DICER1-related disorders.

\(^f\)Testing for Ashkenazi Jewish founder-specific mutation(s) should be performed first. Comprehensive genetic testing may be considered if ancestry also includes non-Ashkenazi Jewish relatives or if other BRCA-related criteria are met. Founder mutations exist in other populations.

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**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
NICE Guidelines (UK) June 2013

• Carrier probability at which genetic testing should be offered

• Breast/ovarian cancer cases with combined BRCA1/BRCA2 mutation carrier probability of ≥10% (based on acceptable methods)

• NICE 2013 guidelines indicate that research is needed on the benefits and harms of RGCT (Rapid Genetic Counseling and Testing)
Who should we test for gBRCA mutations?

- From classical genetics to genetically-driven precision medicine...
- Current guidelines (historical target: 10% tested positive; use family history, male cancer, ovarian cancer, TNBC < 50 or 60, age < 40, askenazi descent) identify only part of the carriers.
- Risk-benefit of testing to be re-estimated provided targeted therapeutic benefit is relevant.

What is risk?? VUS, cost...

Courtesy of Karen Gelmon
Consider genetic counseling & testing when:

- Bilateral breast cancer
- Early onset breast cancer (≤40-45)
- Histo-pathologic features including: triple negative subtype (Medullary carcinoma, lymphocytic infiltration)
- Personal or family history of – breast (incl. male breast cancer), ovarian, pancreatic or prostate cancer
- Certain ethnic groups (eg Ashkenazi Jewish ancestry)
Genetic counseling
- what, how, when?
Genetic counseling for inherited cancer predisposition

Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease*

Who *can* give genetic counseling?

- **USA** – Physicians and genetic counselors (*relatively new profession, MSc to PhD; ABGC*)

- **Europe** – also “genetic nurses”

- **Israel** – *Genetic Information Law (2001)*: Physicians within their specialty and genetic counselors.
Genetic counseling for inherited cancer predisposition

Affected vs. Healthy

Common issues:
• Risk assessment for specific cancers.
• Cancer surveillance and prevention.
• Familial implications: mode of inheritance, relatives at risk, reproduction.
• Genetic testing: sensitivity, clinical utility, method, result interpretation.

Issues for affected women:
• Therapeutic implications – Surgical & Medical.
• Recently diagnosed – time pressure & information overload
• Reproductive
Genetic counseling for inherited cancer predisposition

The traditional model:

- **Pretest counseling (30-45 min, and more)**
  - Drawing a family pedigree
  - Discussion – inheritance, risk assessment, etc.
  - Reaching an informed decision about testing.

- **Genetic testing**

- **Post-test counseling (variable length)**
  - Discussion of results
  - Recommendations for patient and relatives
Genetic Counseling - Issues

- Different national requirements and institutional policies
- Could be a bottleneck to timely testing
- New studies suggesting that written information or post-testing counseling as acceptable alternative
Genetic testing in the young patient – what is the right time?

The question is not *if* to test, but *when* to test
BRCA1/ BRCA2 testing at breast cancer diagnosis:

Potential concerns

• Information overload
• Psychological distress
• Delay in treatment initiation — if testing takes too long.
### Rapid vs. Traditional BRCA testing in patients at Modena Cancer Genetics Clinic

<table>
<thead>
<tr>
<th></th>
<th>Traditional</th>
<th>Rapid</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uptake</td>
<td>70% (1058/1520)</td>
<td>100% (110/110)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>BRCA1/B RCA2 positive</td>
<td>20% (209/1058)</td>
<td>33% (36/110)</td>
<td>.003</td>
</tr>
<tr>
<td>RRM in BRCA positive</td>
<td>4.7% (10/209)</td>
<td>42% (15/36)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Contralateral disease by pathology @ RRM</td>
<td>20% (2/10)</td>
<td>27% (4/15)</td>
<td>NS</td>
</tr>
<tr>
<td>Psychological support usage post RRM (voluntary)</td>
<td>50% (5/10) Age: 38y (SD = 7y)</td>
<td>53% (8/15) Age: 37y (SD = 6y)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Conclusions — Modena Cancer Clinic Study

Rapid genetic testing:
- Increased uptake of testing
- Identification of more carriers (higher rate)
- Increased uptake of contralateral RRM
- No increased use of psychological support services
Psychological implications - Rapid genetic testing

- Immediate effects: 54% (18/26) reported distress beyond that generated by cancer diagnosis (not associate with test results) 19% (5/26) reported rapid testing reduced their distress.
- Long term (2.5y) status: 23% (6/26) had clinically relevant breast cancer –specific distress (IES>25) (comparable to historical controls).
- Satisfaction: 96% (25/26) very/satisfied with rapid testing. 88% thought best timing was between diagnosis and surgery.

- No long term harm (Baers et al Clin Genet 2014, testing performed during radiotherapy)
How BRCA testing may change with the introduction of specific BRCA therapies?

• More patients referred for testing

• Quicker results needed

• Testing may take place earlier - at diagnosis or during early treatment phase

• Role/timing of counselling may change
Hereditary breast cancer syndrome & multi-gene panel testing
Other HBOC Syndromes

- Li Fraumeni Syndrome
- $p53$ mutation
- $PTEN$/Cowden Syndrome
- $ATM$ mutation
- Lynch Syndrome
- $MLH1$, $MSH2$, $MSH6$, $EPCAM$ and $PMS2$ mutations
- $RAD51$ mutation
- $BRIP1$ mutation
- $PALB2$ mutation
- $CHEK2$ mutation
- $STK11$ mutation
- (Peutz-Jeghers Syndrome)
- $CDH1$ mutation

Clinical implications for prevention and screening not well understood for all these mutations…..
NCCN Guidelines Version 2.2017
BRCA-Related Breast and/or Ovarian Cancer Syndrome

BRCA-RELATED FOLLOW-UP

FAMILY STATUS

GENETIC TESTING

TEST OUTCOME

SCREENING RECOMMENDATION

BRCA testing criteria met

Deleterious familial BRCA1/BRCA2 mutation known

Recommend BRCA1/BRCA2 testing for specific familial mutation

Positive for familial BRCA1/BRCA2 mutation

See BRCA-Related Mutation-Positive Management (BRCA-A)

BRCA1/BRCA2 testing not performed

Negative for familial BRCA1/BRCA2 mutation

Cancer screening as per NCCN Screening Guidelines

No known familial BRCA1/BRCA2 mutation

Consider comprehensive BRCA1/BRCA2 testing of patient or if unaffected, test family member with highest likelihood of a mutation

Mutation found

Consider multi-gene testing, if appropriate

See Multi-Gene Testing (GENE-1)

Not tested

No mutation found

Variant of unknown significance found (uninformative)

For both affected and unaffected individuals of Ashkenazi Jewish descent with no known familial mutation, first test for the three common mutations. Then, if negative for the three mutations and ancestry also includes non-Ashkenazi Jewish relatives or other BRCA-related criteria are met, consider comprehensive genetic testing. For both affected and unaffected individuals who are non-Ashkenazi Jewish and who have no known familial mutation, comprehensive genetic testing is the approach, if done.

If no mutation found, consider testing another family member with next highest likelihood of having a mutation and/or other hereditary breast/ovarian cancer syndromes such as Li-Fraumeni (LIFR-1) and/or Cowden syndrome (COWD-1) or multi-gene testing (GENE-1). For additional information on other genetic mutations associated with breast/ovarian cancer risk for which genetic testing is clinically available, see GENE-2.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
Cancer Risk Variants

 Allele Frequency

 Common Variants

 Single nucleotide polymorphisms

 CHEK2, ATM, NBN

 Rare variants (moderate)

 BRCA1, BRCA2, TP53

 Rare variants (high)

 Relative Risk

 1 2 5 ≥10
Results from Genetic Testing

• **Positive**
  – Deleterious mutation identified

• **Negative**
  – Interpretation differs if a mutation has previously been identified in the family
    • Mutation known – true negative
    • Mutation unknown – uninformative

• **Variant of unknown significance**
  – Significance will depend on how variant tracks through family - i.e. is variant present in people with disease?
  – Can use databases to check previous reports
Why do this?

• If it’s clinically indicated!
• More cost effective (for the testing) to do multigene rather than serial testing
• Patients (and providers!) can get testing fatigue
• The same cancer can be seen in different hereditary syndromes
  – Ovarian cancer in both BRCA1/2 and Lynch
  – Uterine cancer in Lynch and Cowden
  – Breast in Li-Fraumeni and BRCA1/2
NGS Panels- Breast

• 800 families with negative BRCA1/2 testing
  – 206 tested positive with NGS BROCA panel (26%)

• Of the 26% with a new positive results
  – 39% (80/206) had BRCA1/2 mutations
  – 37% carried mutations in CHEK2, PALB2, or TP53
  – 20% carried mutations in 10 less characterized genes

Walsh et. al. 2013
This has become very complicated....
What is the risk (penetrance)?
Increased risk of other cancers:

- Male breast cancer  
- Pancreatic cancer  
- Prostate cancer  
- Melanoma  

Breast cancer: 50%-70%

Second primary breast cancer: 40%-50%

Ovarian cancer: 15-45% \( BRCA_1 > BRCA_2 \)

Increased risk of other cancers:

- Male breast cancer  
- Pancreatic cancer  
- Prostate cancer  
- Melanoma  

Different definitions of “lifetime” yield different outcomes

“Remaining lifetime risk” higher for younger patients
Cumulative Risks of Breast and Ovarian Cancer in \textit{BRCA1,2} Carriers

Figure 2. Estimated Cumulative Risks of Breast and Ovarian Cancer in Mutation Carriers

Kuchenbacker, JAMA 2017
### Lifetime risk of breast cancer

TABLE 2. Estimated lifetime risk of breast cancer associated with selected susceptibility genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Estimated lifetime risk of breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>55-65%(^{10})</td>
</tr>
<tr>
<td>BRCA2</td>
<td>45-47%(^{13})</td>
</tr>
<tr>
<td>TP53</td>
<td>49-60%(^{36})</td>
</tr>
<tr>
<td>PTEN</td>
<td>25-50%(^{61,62})</td>
</tr>
<tr>
<td>PALB2</td>
<td>33-58%(^{56})</td>
</tr>
<tr>
<td>STK11</td>
<td>30-50%(^{58,63,64})</td>
</tr>
<tr>
<td>CDH1</td>
<td>39-52%(^{65,66})</td>
</tr>
<tr>
<td>ATM</td>
<td>15-52%(^{67-70})</td>
</tr>
<tr>
<td>CHEK2</td>
<td>20-44%(^{71-74})</td>
</tr>
</tbody>
</table>
Average estimated cumulative 5-year and lifetime breast cancer risks

<table>
<thead>
<tr>
<th>Age</th>
<th>5 year</th>
<th>Cumulative</th>
<th>5 year</th>
<th>Cumulative</th>
<th>5 year</th>
<th>Cumulative</th>
<th>5 year</th>
<th>Cumulative</th>
<th>5 year</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-29</td>
<td>0.04%</td>
<td>0.1%</td>
<td>0.12%</td>
<td>0.1%</td>
<td>0.13%</td>
<td>0.2%</td>
<td>0.07%</td>
<td>0.1%</td>
<td>0.35%</td>
<td>0.4%</td>
</tr>
<tr>
<td>30-34</td>
<td>0.14%</td>
<td>0.2%</td>
<td>0.38%</td>
<td>0.5%</td>
<td>0.41%</td>
<td>0.6%</td>
<td>0.21%</td>
<td>0.3%</td>
<td>1.05%</td>
<td>2%</td>
</tr>
<tr>
<td>35-39</td>
<td>0.30%</td>
<td>0.5%</td>
<td>0.84%</td>
<td>1.4%</td>
<td>0.90%</td>
<td>1.5%</td>
<td>0.48%</td>
<td>0.8%</td>
<td>2.5%</td>
<td>4%</td>
</tr>
<tr>
<td>40-44</td>
<td>0.61%</td>
<td>1.1%</td>
<td>1.70%</td>
<td>3.0%</td>
<td>1.83%</td>
<td>3.2%</td>
<td>0.96%</td>
<td>1.7%</td>
<td>4.25%</td>
<td>8%</td>
</tr>
<tr>
<td>45-49</td>
<td>0.94%</td>
<td>2.0%</td>
<td>2.64%</td>
<td>5.6%</td>
<td>2.83%</td>
<td>5.9%</td>
<td>1.49%</td>
<td>3.2%</td>
<td>6.35%</td>
<td>14%</td>
</tr>
<tr>
<td>50-54</td>
<td>1.12%</td>
<td>3.1%</td>
<td>3.14%</td>
<td>8.5%</td>
<td>3.36%</td>
<td>9.1%</td>
<td>1.77%</td>
<td>4.9%</td>
<td>8.00%</td>
<td>20%</td>
</tr>
<tr>
<td>55-59</td>
<td>1.33%</td>
<td>4.4%</td>
<td>3.71%</td>
<td>11.8%</td>
<td>3.98%</td>
<td>12.6%</td>
<td>2.09%</td>
<td>6.8%</td>
<td>7.25%</td>
<td>26%</td>
</tr>
<tr>
<td>60-64</td>
<td>1.72%</td>
<td>6.0%</td>
<td>4.81%</td>
<td>16.0%</td>
<td>5.15%</td>
<td>17.0%</td>
<td>2.71%</td>
<td>9.3%</td>
<td>7.35%</td>
<td>31%</td>
</tr>
<tr>
<td>65-69</td>
<td>2.11%</td>
<td>8.0%</td>
<td>5.92%</td>
<td>20.8%</td>
<td>6.34%</td>
<td>22.1%</td>
<td>3.34%</td>
<td>12.3%</td>
<td>5.95%</td>
<td>35%</td>
</tr>
<tr>
<td>70-75</td>
<td>2.20%</td>
<td>10.0%</td>
<td>6.17%</td>
<td>25.5%</td>
<td>6.61%</td>
<td>27.1%</td>
<td>3.48%</td>
<td>15.3%</td>
<td>6.70%</td>
<td>40%</td>
</tr>
<tr>
<td>CLTR (80)</td>
<td>2.24%</td>
<td>12.0%</td>
<td>30.0%</td>
<td>31.8%</td>
<td>18.3%</td>
<td>44%</td>
<td></td>
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</tr>
</tbody>
</table>

TUNG, NATURE REVIEWS CLINICAL ONCOLOGY, 2016
Considerations in the health BRCA carrier
Risk reduction & screening

- Risk reducing surgery
  - Bilateral RRM
  - RRSO
- Chemoprevention
- Lifestyle intervention
- Screening for early detection:
  ✓ Breast & Ovarian cancer
  ?? Pancreatic cancer, prostate cancer
REPRODUCTIVE ISSUES
Reproductive considerations in BRCA mutation carriers

| BRCA1/2 carriers can be reassured that there is no convincing evidence that mutation carriers have reduced ovarian reserve or fertility |
| All women harbouring a BRCA1/2 mutation should be encouraged to complete child-bearing prior to planned RRSO |
| For women who wish to undergo RRSO and have not yet completed child-bearing fertility preservation options should be discussed |
| BRCA1/2 mutation carriers (male and female) planning to conceive should be made aware of the options of pre-natal diagnosis (via chorio-villous or amniotic fluid sampling in week 11-20 of gestation) and PGD |
| Women harbouring a BRCA1/2 mutation who have been diagnosed with a malignancy should be counselled about options for fertility preservation prior to the commencement of oncology treatment |
| Appropriate counselling should be available and vaginal moisturisers and lubricants should be prescribed to all women following RRS |
| Short term use of HRT to alleviate menopausal symptoms following RRSO is safe amongst healthy BRCA1/2 mutation carriers |
| No safety data are available about the use of HRT amongst BRCA1/2 carriers with a previous diagnosis of breast cancer. The relationship between hormonal influences and the development of different breast cancer subtypes, including triple negative breast cancers, has not been fully elucidated thus HRT in the setting of a past breast cancer diagnosis should be strongly discouraged – irrespective of endocrine status of the initial tumour |
| Topical oestrogens to alleviate vaginal dryness may be used with caution |
| As a result of premature menopause, bone health needs to be routinely monitored, preventive measures taken and any reduction in bone density treated as clinically indicated |

Reproductive issues

• Timing of RRSO (risk reducing oophorectomy)
  - For BRCA1 – between 35-40
  - For BRCA2 – 40-45

• Fertility preservation

• PGD – pre-implantation genetic diagnosis

• Premature menopause – impact on sexual health, bone health, quality of life
Management of Mutation Carriers

Consider...

• **Psychosocial support to assist with:**
  – Adjusting to new information
    • most adjust within 3-6 months
    • subset remain psychologically distressed (16-25% anxiety and/or depression)
  – Making decisions regarding management
    “to inflict surgery is a hard decision to make... when I don’t have the disease and feel healthy”
  – Addressing family issues, self concept, body image
  – Dealing with future concerns i.e. child bearing, surgical menopause after oophorectomy

• **Referral to support groups**
Future questions

• Prevention studies using novel agents
• Risk-reducing irradiation of contralateral breast – Israeli study – ongoing
• Role of PARPi for carriers of mutations of genes (proteins) involved in DNA repair pathways
• ABCSG prevention study – 2018 Q1
Future directions

• Population screening
• Further understanding of genetic and non-genetic risk modifiers to personalise risk assessment and tailor recommendations for screening and risk-reducing measures
  For example: ovarian-cancer-cluster-regions and breast-cancer-cluster-regions that modify risk of OC or BC
• whole exome/genome studies may bring further insights into risk modification
In summary:
Unique challenges in BRCA1/2 associated BC

- Multitude of therapeutic & reproductive decisions
- Knowledge of BRCA1/2 status may arrive at a time of great distress
- Risk reducing measures are often an assault on self-image, “womanhood”
- Far reaching implications for family planning and for the extended family
- Multiple psychosocial issues - support is imperative
- **Multi-disciplinary care – is a MUST**
Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening†

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Thank you