Hereditary Breast/Ovarian Cancer Syndrome (HBOC): A Geneticist’s Perspective

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Disclosure:

• Nothing to disclose
Objectives:

• To outline a specialized cancer risk assessment clinic

• How to select possible candidates for cancer risk assessment and specialized screening tests as shown by EBM

• To devise an algorithm and a step-by-step close follow up plan for high risk patients based on ACMG/NCCN guidelines
Note:

• Hereditary Breast/Ovarian Cancer high risk screening as a model for other inherited cancers and syndromes.

• Since BRCA1 and 2 mutations comprise ~50% of inherited breast cancers, and for simplicity and time saving, the talk will be focused on BCRA1&2 mutations.
Epidemiology of Breast and Ovarian Cancers

• About 13 percent of women in the general population will develop breast cancer sometime during their lives.

• Together, BRCA1 and BRCA2 mutations account for 5%-10% of all breast cancers.

• Mutations in BRCA1 and BRCA2 account for around 15 percent of ovarian cancers overall.

• The lifetime risk for these cancers in individuals with a pathogenic variant in BRCA1 or BRCA2:
  • 40%-80% for breast cancer
  • 11%-40% for ovarian cancer
  • 1%-10% for male breast cancer
  • Up to 39% for prostate cancer
  • 1%-7% for pancreatic cancer

Epidemiology of Male Breast Cancer:

- A lifetime risk of approximately 0.1% for breast cancer in men in the general population.

- Men with a BRCA1 mutation have an approximate 1-2% risk of breast cancer.

- Men with a BRCA2 gene mutation, the lifetime risk of breast cancer is approximately 5-10% percent.

Other cancers associated with BRCA1 and 2:

- **Fallopian tube** (J Clin Oncol. 2003;21(22):4222.)
- **Peritoneum** (J Clin Oncol. 2003;21(22):4222.)
- **Prostate** (BJU Int. 2011;107(1):28.)
- **Colorectal cancer** (Br J Cancer. 2014 Jan;110(2):530-4. Epub 2013 Nov 28.)
- **Pancreas** (J Natl Cancer Inst. 1999;91(15):1310.)
- **Stomach and biliary** (J Natl Cancer Inst. 1999;91(15):1310.)
- **Uterus** (Gynecol Oncol. 2007;104(1):7.)
Germline mutation of BRCA1:

The Breast Cancer Linkage Consortium reported statistically significantly increased relative risks for cancers of the pancreas, uterine body and cervix (only in heterozygous women age <65 years), with relative risks of 2.3, 2.6, and 3.7 respectively [Thompson & Easton 2002].

Germline mutation of BRCA2:

The Breast Cancer Linkage Consortium reported statistically increased relative risks for cancers of the gallbladder, bile duct, stomach, and melanoma with relative risks of 3.5, 5.0, 2.6, and 2.6 respectively, the latter three sites being inconsistently associated with BRCA2 [van Asperen et al 2005].

http://www.ncbi.nlm.nih.gov/books/NBK1247/
A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment

<table>
<thead>
<tr>
<th>Condition</th>
<th>Indications</th>
<th>Code/OMIM Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer, female</td>
<td>Breast cancer dx at age ≤50</td>
<td>HBOC, OMIM: 604370, 612555; LFS, OMIM 151623</td>
</tr>
<tr>
<td></td>
<td>Triple-negative breast cancer dx at age ≤60</td>
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<td>≥2 primary breast cancers in the same person</td>
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<tr>
<td></td>
<td>Ashkenazi Jewish ancestry and breast cancer at any age</td>
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<tr>
<td></td>
<td>≥3 cases of breast, ovarian, pancreatic, and/or aggressive prostate cancer in close relatives, including the patient</td>
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<tr>
<td></td>
<td>Breast cancer and one additional LFS tumor (Table 5) in the same person or in two relatives, one dx at age ≤45</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Breast cancer and ≥1 PJ polyp in the same person</td>
<td>PJS, OMIM 175200</td>
</tr>
<tr>
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<td>Lobular breast cancer and diffuse gastric cancer in the same person</td>
<td>HDGC, OMIM 137215</td>
</tr>
<tr>
<td></td>
<td>Lobular breast cancer in one relative and diffuse gastric cancer in another, one dx at age ≤50</td>
<td></td>
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<tr>
<td></td>
<td>Breast cancer and two additional Cowden syndrome criteria (Table 4) in the same person</td>
<td>Cowden, OMIM 158350</td>
</tr>
<tr>
<td>Breast cancer, male</td>
<td>Single case present</td>
<td>HBCO, OMIM: 604370, 612555</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>Colorectal cancer dx at age &lt;50</td>
<td>LS, OMIM 120435, 120436; CMMRD, OMIM 276300; MAP, OMIM 608456</td>
</tr>
<tr>
<td></td>
<td>Colorectal cancer dx at age ≥50 if there is a FDR with colorectal or endometrial</td>
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</tbody>
</table>

BRCA-Related Breast and/or Ovarian Cancer Syndrome

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

- Personal history of prostate cancer (Gleason score ≥7) at any age with ≥1 close blood relative with breast and/or ovarian carcinoma and/or pancreatic or prostate cancer (Gleason score ≥7) at any age
- Personal history of pancreatic cancer at any age with ≥1 close blood relative with breast and/or ovarian carcinoma and/or prostate cancer (Gleason score ≥7) at any age
- Personal history of pancreatic cancer and Ashkenazi Jewish ancestry
- Family history only (significant limitations of interpreting test results for an unaffected individual should be discussed):
  - First- or second-degree blood relative meeting any of the above criteria
  - Third-degree blood relative who has breast cancer and/or ovarian carcinoma and who has ≥2 close blood relatives with breast cancer (at least one with breast cancer ≤60 y) and/or ovarian carcinoma

See Follow-up (BRCA-2)

If criteria for other hereditary syndromes not met, consider testing for other hereditary syndromes

If BRCA testing criteria not met, consider screening as per NCCN Screening Guidelines

NOTE:
- 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.
- 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.
Patients in whom hereditary breast cancer should be suspected:

- Breast cancer diagnosed ≤ 45 years.
- Bilateral breast cancer or Multiple breast cancers in the same person.
- More than two family members with primary types BRCA1&2 cancers on the same side of the family.
- Two or more primary types of BRCA1&2-related cancers in a single family member
- Women with ovarian cancer at any age.
- Women ≤60 years of age with triple negative breast cancer.
- Men with breast cancer at any age.
Hereditary Cancer Clinic, Dr. S. Bahzad

1. The Hereditary Cancer Clinic is a once-a-week clinic on Wednesdays at the Kuwait Cancer Control Centre (KCCC).
2. Choose a primary cancer type with which the patient or a member of the family has been diagnosed.
3. Fill in patient's information. Phone number and e-mail address are required.
4. Receive a confirmation.
5. Please reschedule or cancel if you feel you cannot make it to the appointment.

I would like to schedule...
- Breast Cancer
  1 hour
- Colorectal Cancer
  1 hour
- Oesophageal Cancer
  1 hour
- Cervical Cancer
  1 hour
- Gastrointestinal Cancer
  1 hour
- Other types of cancer
  1 hour

Appointment Booking is powered by Acuity Scheduling
Hereditary Cancer Clinic, Dr. S. Bahzad

Choose Appointment  Your Info  Confirmation

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Breast Cancer
1 hour

Appointment Booking is powered by Acaley Scheduling
Hereditary Cancer Clinic, Dr. S. Bahzad

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2. Choose a primary cancer type with which the patient or a member of the family has been diagnosed.
3. Fill in patient's information. Phone number and e-mail address are required.
4. Receive a confirmation.
5. Please reschedule or cancel if you feel you cannot make it to the appointment.

Appointment Booking is powered by Acuity Scheduling
Hereditary Cancer Clinic, Dr. S. Bahzad

Choose Appointment

Breast Cancer (1 hour) on May 18, 2016 at 9:00am

Name *
First Last

Phone *

E-mail *

Complete Appointment »

Appointment Booking is powered by Acuity Scheduling
Hereditary Cancer Clinic, Dr. S. Bahzad

Breast Cancer
Wednesday, May 18, 2016
9:00am AST
Hereditary Cancer Clinic, Dr. S. Bahzad

1. Please bring all reports, test results, and referral letter to your appointment.
2. Please reschedule or cancel if you think you cannot make it to the appointment.
3. To provide a better service, please be at the clinic 10 minutes prior to your appointment.

Appointment Booking is powered by Acuity Scheduling
At the Hereditary Cancer Clinic:

- History of present illness and past medical history
- Pedigree
- Hereditary cancer and testing counseling (Pre- and post testing counselling)
- Eligibility-for-testing discussion
- Risk calculation
History of present illness and past medical history:

- Has/had cancer?
- Which type?
- At what age?
- How many primaries?
- Pathology report(s)?
- Received chemo- or radio-therapy?
- Any members of the family previously tested? Can we get a copy of the report?
Family: Hughes
Pedigree No.: 5643
Ethnicity: Irish, Scottish
Date Drawn: February 6th 2015

Legend
- Breast Cancer
- Prostate Cancer
- Unknown Cancer
- Ovarian Cancer
- New Entry...
Pre-testing Genetics Counseling:

- Genetic counseling is done before and after any genetic test for an inherited cancer syndrome.

- Counseling should be performed by a health care professional who is experienced in cancer genetics.

- Genetic counseling usually covers many aspects of the testing process, including:

  1- A hereditary cancer risk assessment based on an individual’s personal and family medical history.

  2- Discussion of:

- The appropriateness of genetic testing
- The medical implications of a positive, unknown significance, and a negative test result
- The possibility that a test result might not be informative
- The psychological risks and benefits of genetic test results
- The risk of passing a mutation to children (eg. Inheritance, expressivity ....)
- Explanation of the specific test(s) that might be used and the technical accuracy of the test(s)
Eligible for testing:

• Offer the test

Not eligible for testing:

• Do risk calculation
Calculating Breast Cancer Risk (without genetic testing):

• Using risk assessment tools (software) to assess the probability of developing breast cancer and carrying a BRCA gene mutation.

• IBIS or BOADICEA

• With IBIS, will calculate 10-year risk and lifetime risk of breast cancer

• With BOADICEA, will calculate 5-year risk and lifetime risk of breast cancer
IBIS Breast Cancer Risk Evaluation Tool

http://www.ems-trials.org/riskevaluator/
Evaluation Screen
A typical personal entry
Family History Section
A worked example
After pressing the ‘calculate risk’ button
Age of person is 47 years.
Age at menarche was 12 years.
Age at first birth was 24 years.
Person is premenopausal.

Risk after 10 years is 6.64%.
10 year population risk is 2.389%.
Lifetime risk is 20.82%.
Lifetime population risk is 8.826%.
Probability of a BRCA1 gene is 4.458%.
Probability of a BRCA2 gene is 2.041%.
BRCA-Related Breast and/or Ovarian Cancer Syndrome

BRCA MUTATION-POSITIVE MANAGEMENT

WOMEN
- Breast awareness starting at age 18 y.
- Clinical breast exam, every 8–12 mo, starting at age 25 y.
- Breast screening:
  - Age 25–29 y, annual breast MRI screening (preferred) or mammogram if MRI is unavailable or individualized based on family history if a breast cancer diagnosis before age 30 is present.
  - Age 30–75 y, annual mammogram and breast MRI screening.
  - Age >75 y, management should be considered on an individual basis.
- For women with a BRCA4 mutation who are treated for breast cancer, screening of remaining breast tissue with annual mammography and breast MRI should continue.
- Discuss option of risk-reducing mastectomy
  - Counseling may include a discussion regarding degree of protection, reconstruction options, and risks.
  - Recommend risk-reducing salpingo-oophorectomy (RRSO) typically between 35 and 40 y, and upon completion of child bearing. Because ovarian cancer onset in patients with BRCA1 mutations is an average of 8–10 years later than in patients with BRCA1 mutations, it is reasonable to delay RRSO until age 40–45 y in patients with BRCA2 mutations who have already maximized their breast cancer prevention (i.e., undergone bilateral mastectomy). See Risk-Reducing Salpingo-Oophorectomy (RRSO) Protocol in NCCN Guidelines for Ovarian Cancer: Principles of Surgery.
  - Counseling includes a discussion of reproductive desires, extent of cancer risk, degree of protection for breast and ovarian cancer, management of menopausal symptoms, possible short-term hormone replacement therapy to a recommended maximum age of natural menopause, and related medical issues.
  - Salpingectomy alone is not the standard of care for risk reduction although clinical trials are ongoing. The concern for risk-reducing salpingectomy alone is that women are still at risk for developing ovarian cancer. In addition, in premenopausal women, oophorectomy reduces the risk of developing breast cancer by up to 60% depending upon age of procedure.
  - Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy and/or salpingo-oophorectomy.
  - For those patients who have not elected RRSO, while there may be circumstances where clinicians find screening helpful, data do not support routine ovarian screening. Transvaginal ultrasound for ovarian cancer has not been shown to be sufficiently sensitive or specific as to support a positive recommendation, but may be considered at the clinician’s discretion starting at age 30–35 y. Serum CA-125 is an additional ovarian screening test with caveats similar to transvaginal ultrasound.
  - Consider risk reduction agents as options for breast and ovarian cancer, including discussing risks and benefits (See Discussion for details).
  - (See NCCN Guidelines for Breast Cancer Risk Reduction)
  - Consider investigational imaging and screening studies, when available (e.g., novel imaging technologies, more frequent screening intervals) in the context of a clinical trial.

1Women should be familiar with their breasts and promptly report changes to their health care provider. Periodic, consistent breast self exam (BSE) may facilitate breast self awareness. Premenopausal women may find BSE most informative when performed at the end of menses.

2Randomized trials comparing clinical breast exam versus no screening have not been performed. Rational for recommending clinical breast exam every 6–12 mo is the concern for internal breast cancers.


4High-quality breast MRI limitations include having a need for a dedicated breast coil, the ability to perform biopsy under MRI guidance, experienced radiologists in breast MRI, and regional availability. Breast MRI is performed preferably days 7–15 of menstrual cycle for premenopausal women.

5Given the high rate of occult neoplasms, special attention should be given to sampling and pathologic review of the ovaries and fallopian tubes. (See Discussion for details.)

6See the College of American Pathologists, Protocol for the Examination of Specimens from Patients with Carcinoma of the Ovary. See NCCN Guidelines for Ovarian Cancer for treatment of findings.
Other Hereditary Syndromes Associated with Breast/Ovarian Cancers

Li-Fraumeni Syndrome (LFS):
• TP53 gene
• Sarcomas: 25%
• Breast Cancer: 6 times the general population

Cowden Syndrome (CS):
• PTEN gene
• Breast Cancer: 85%
• Thyroid Cancer: 35%
• Endometrial Cancer: 28%

Hereditary Diffuse Gastric Cancer Syndrome:
• CDH1 gene
• Diffuse gastric cancer: 67% - 83%
• Lobular cancer of the breast: 39%-52%
Other Hereditary Syndromes Associated with Breast/Ovarian Cancers

Lynch Syndrome (LS):
•Mismatch Repair (MMR) genes – MLH1, MSH2, MSH6, PMS2
•EPCAM gene deletion
•Colorectal cancer
•Ovarian Cancer: 9%
•Breast Cancer: conflicting data regarding increased risk

Peutz-Jeghers Syndrome (PJS):
•STK11/LKB1 gene gene
•Breast Cancer: 44-50%
•Ovarian Cancer: 18-21% (ovarian sex cord are the most common)
<table>
<thead>
<tr>
<th>Intervention warranted based on gene and/or risk level</th>
<th>Recommend Breast MRI&lt;sup&gt;d&lt;/sup&gt; (&gt;20% risk of breast cancer&lt;sup&gt;a&lt;/sup&gt;)</th>
<th>Discuss Option of RRM</th>
<th>Recommend/Consider RRSO</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, STK11, TP53</td>
<td>BRCA1, BRCA2, CDH1, PTEN, TP53, PALB2</td>
<td>BRCA1, BRCA2, Lynch syndrome&lt;sup&gt;f&lt;/sup&gt;, BRIP1, RAD51C, RAD51D</td>
<td></td>
</tr>
<tr>
<td>Insufficient evidence for intervention&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>BRIP1</td>
<td>ATM, CHEK2, STK11</td>
<td>PALB2</td>
</tr>
</tbody>
</table>

RRM: risk-reducing mastectomy  
RRSO: risk-reducing salpingo-oophorectomy
Step 7: Report:

**What will the referring physician get in the “Dear Doctor Letter”?**

1. Patient’s history and medical information.
2. Pedigree
3. Risk assessment (lifetime, 5 year, and 10 year)
4. Eligible/Not Eligible for High Risk Screening Program with explanation
5. Eligible/Not eligible for BRCA1&2 (or gene panel) testing with explanation
6. BRCA1&2 (or gene panel) results with interpretation
7. Summary of the genetic counseling session
8. Recommendations, references, referrals
References:

• PATH report estimated the total proportion of Ontario females eligible for screening was 0.95% for risk groups 1, 2, 3 and 4. See Blackhouse, Gord and Ron Goeree. Budget Impact Analysis for Magnetic Resonance Imaging Screening of Women at High Risk for Breast Cancer in Ontario. Program for Assessment of Technology in Health (PATH). May 8, 2007.
THANK YOU!

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