GEC KO Messenger
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HEREDITARY BREAST AND OVARIAN CANCER

Bottom line: Breast cancer is relatively common in the general population (12% lifetime risk) and the majority of cases occur sporadically. About 5-10% of breast cancer is due to an inherited gene change. Mutations in the genes *BRCA1* or *BRCA2* are the most common cause of hereditary breast and ovarian cancer (HBOC) and *BRCA1* and *BRCA2* mutation carriers have a significant increased lifetime risk for breast and ovarian cancer in addition to other cancers. Risk-reducing surgeries and, for some women, chemoprevention, can reduce mortality from breast and ovarian cancers in both *BRCA1* and *BRCA2* carriers. Individuals with family histories of breast or ovarian cancer that are at high risk (generally >10%) to carry a *BRCA1* or *BRCA2* gene mutation can be offered referral to genetics services for a discussion of the benefits, harms and limitations of genetic testing, while women whose family histories suggest a low risk of carrying a *BRCA1* or *BRCA2* gene mutation, can be reassured and offered screening following provincial guidelines. This GECKO Messenger will chiefly focus on HBOC caused by mutations in *BRCA1* or *BRCA2.*

WHAT IS HEREDITARY BREAST AND OVARIAN CANCER SYNDROME?

Approximately 80% of breast cancer occurs sporadically. About 10-15% of breast cancer is familial (when shared familial risk factors e.g. genes, environment, cause a higher incidence of cancer) and about 5-10% is hereditary (due to a single gene mutation). Harmful mutations in *BRCA1* and *BRCA2* appear to account for ~30% of high-risk breast cancer families. There are other hereditary cancer syndromes that cause an increased risk of breast and/or ovarian cancer. [1]

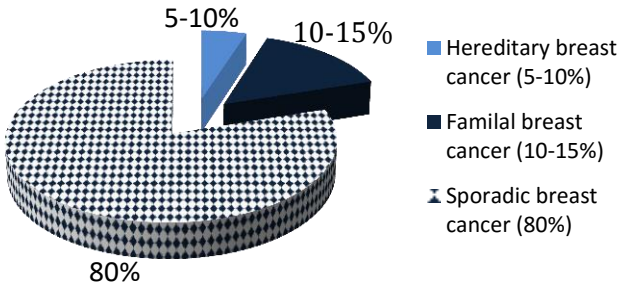

Figure 1. Distribution of breast cancer etiology.

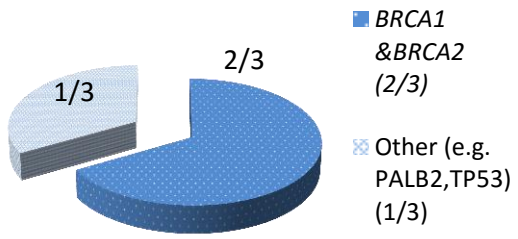

Figure 2. Proportion of genes contributing to hereditary breast cancer

WHAT DO I NEED TO KNOW ABOUT THE GENETICS OF HBOC?

More than 2600 pathogenic mutations have been found in the *BRCA1* and *BRCA2* genes, both of which are tumour suppressor genes. A mutation in one of these genes leads to the inability of a cell to regulate apoptosis (cell death) and to uncontrolled cell growth leading to cancer.

It is estimated that the general population prevalence of pathogenic mutations in the *BRCA1* and *BRCA2* genes is 1 in 300 to 1 in 500[2]. Founder mutations are observed in individuals of Ashkenazi Jewish ethnicity occurring at an estimated frequency of about 1 in 50[2].

PATTERN OF INHERITANCE

HBOC is an autosomal dominant cancer predisposition syndrome. Individuals with HBOC have a high risk for breast and ovarian cancers and a moderate risk for other cancers (Table 1). Not all individuals who inherit a mutation in

BRCA1 or *BRCA2* will develop cancer (*reduced penetrance*) and the signs and symptoms, type, and age of onset of cancer will vary within families (*variable expressivity*).

WHO SHOULD BE OFFERED GENETIC TESTING?

Usually the decision to offer genetic testing is made in the setting of a genetics consult at a hereditary cancer program or a general genetics clinic. Click to connect to your local genetics centre or hereditary cancer program.

If possible, testing is first offered to the **affected** individual in the family at **highest risk to carry a mutation** in order to maximize the likelihood of detecting a mutation. For example, this might be the youngest individual with breast cancer in a family with multiple cases of breast and ovarian cancer.

HOW DO I ASSESS MY PATIENT'S RISK?

Family and personal history factors associated with increased risk for Hereditary Breast /Ovarian cancer

These are general guidelines to identify patients at **high risk** for HBOC. You should consider referring your patient to your local genetics centre or hereditary cancer program for further assessment if s/he has a family or personal history of: [2-5, local genetics centres]

- Breast cancer diagnosis at a young age (<35-45 years) [both invasive and ductal carcinoma *in situ*]
- Ovarian cancer at any age [epithelial]
- Male breast cancer
- Multiple primaries in the same individual e.g. bilateral breast cancer (particularly if the diagnosis was before age 50), breast and ovarian cancer
- Breast cancer diagnosis **AND** a family history of two or more additional HBOC-related cancers, including breast, ovarian, prostate (Gleason ≥7) and pancreatic cancer
- High risk ethnicity (Ashkenazi Jewish, Icelandic) and a personal and/or family history of breast, ovarian or pancreatic cancer
- Triple negative breast cancer diagnosed <age 60

OR if s/he has a personal

- Probability of 10% or higher to carry a *BRCA* mutation

Eligibility criteria for genetic testing vary among organizations. In general, criteria are based on clinical features that increase the likelihood of a hereditary cancer susceptibility syndrome.

If possible, the affected individual in the family at highest risk to carry a mutation is offered testing first in order to maximize the likelihood of detecting a mutation.

Testing an unaffected individual should only be considered if an affected individual is not available for testing. There are significant limitations to interpretation of test results in an unaffected individual. Unaffected individuals can be referred for genetic counselling for risk assessment and information. It is important to note that any individual of Ashkenazi Jewish ethnicity or French Canadian ethnicities can be offered genetic testing for the mutations commonly found in these ethnic groups (e.g. 3 common mutations in those of Ashkenazi Jewish ethnicity). A negative result in this situation only rules out those ethnic-specific mutations.

See the GEC-KO point of care tool which can be used in your practice to help identify patients who would benefit from referral to genetics or your local hereditary cancer program. The tool is based on the Referral Screening Tool[6] which was designed for use in primary care settings and demonstrated an overall sensitivity of 81.2% and a specificity of 91.9%.

If your patient does not meet any of the criteria above, but you are suspicious of a hereditary cancer syndrome, consult your local genetics centre or hereditary cancer program. In general, suspicion of a hereditary cancer syndrome should be raised if:

- There are multiple related family members with related cancers
- Cancers occur on the same side of family
- Cancer diagnoses occur at a younger than expected age
- Several generations are affected (demonstrating an autosomal dominant pattern – typical of most hereditary cancer syndromes)
- Multiple primary cancers are diagnosed in same individual, with early age of onset

HOW IS GENETIC TESTING DONE?

Testing for mutations in *BRCA1* and *BRCA2* involves a blood test, which is usually available at regional genetic centres and some cancer centres. The test is covered by most provincial health plans if there is substantial probability of identifying a mutation. If a mutation has already been identified in a family, testing for this specific mutation is available for all at-risk relatives.

WHAT DOES THE GENETIC TEST RESULT MEAN?

If your patient is found to carry a mutation in the *BRCA 1* or *BRCA2* gene, **a positive result**, s/he has an increased lifetime risk to develop certain cancers (Table 1). This also means that family members are at risk of carrying the same mutation and of having similar cancer risks.

If a mutation is not identified in someone from a family with a known mutation, this is **a true negative result**. You can provide reassurance to your patient; however these individuals may still need to follow modified screening recommendations based on their family history and/or personal history factors (e.g. BMI, age at menarche, personal benign breast disease). Consult your local genetics centre or hereditary cancer program.

If a mutation is not identified in an affected patient who has no known familial mutation this result is **uninformative.**

A **variant of uncertain significance (VUS)** could be identified, which is a gene change that has not yet been categorized as benign or as pathogenic. Some variants may be interpreted as 'likely pathogenic', generally meaning greater than 90% certainty of being disease causing.[7] In these instances screening and management may be modified, and other family members may be offered genetic testing to try to track the familial gene change and to see if it is associated with cancer. Variants are periodically re-classified and patients are often encouraged to recontact their genetics clinic to see if this is the case. In some circumstances, genetic testing for other hereditary cancer syndromes may be considered. In both of these circumstances, the diagnosis of HBOC is neither confirmed nor ruled out, especially in families with a strong history of breast and/or ovarian cancer.

Table 1. Significant lifetime cancer risks for individuals who have inherited a mutation in the *BRCA1* or *BRCA2* gene as compared to the general population.

Cancer type	Cancer risk in a mutation carriers of:		General Population
	BRCA1	*BRCA2*	
Invasive Breast (in women)			
Cumulative risk that a woman will be diagnosed with breast cancer during the next 10 years, starting at age 40	20%[8]	15%[8]	1.4%[9]
Cumulative risk that a woman will be diagnosed with breast cancer during the next 10 years, starting at age 60	19%[8]	17%[8]	3.5%[9]
Cumulative lifetime cancer risk (by age 70)	57%[8]	49%[8]	~12%[9]
Ovarian			
Cumulative risk that a woman will be diagnosed with ovarian cancer during the next 10 years, starting at age 40	6.7%[8]	1.9%[8]	0.1%[9]
Cumulative risk that a woman will be diagnosed with ovarian cancer during the next 10 years, starting at age 60	22%[8]	9.8%[8]	0.3%[9]
Cumulative lifetime cancer risk (by age 70)	40%[8]	18%[8]	~1.3%[9]
Breast (male)			
Cumulative lifetime cancer risk (by age 70)	Increased[4,10] (*controversial*)	6-7%[4,10,11]	0.1%[4,10,11]
Prostate			
Lifetime cancer risk (by age 70)	n/a	2-6x increased risk[12-16] Literature suggests more aggressive phenotype (e.g. Gleason 7+) and higher risks before age 65 years	~14%[9]

NOTE: The literature suggests that there is also an increased lifetime risk for other cancers such as melanoma and pancreatic cancer in *BRCA* mutation carriers. [4,15]

HOW DO I ORDER THE GENETIC TEST?

Usually the decision to offer genetic testing is made in the setting of a genetics consult at a hereditary cancer program or general genetics clinic. To assess if your patient could be eligible for genetic testing see Who Should Be Offered Genetic Testing? Click to connect with your local genetics centre or hereditary cancer program and find their referral criteria. If your patient does not have cancer, genetic testing of a relative with cancer will be recommended as a first step.

WHERE DO I REFER MY PATIENT?

Click to connect to your local genetics centre or hereditary cancer program.

Note that hereditary cancer programs/general genetics centres vary with regards to the referrals they choose to accept. You may want to contact your local genetics centre or hereditary cancer program for more information.

Include all relevant information with your referral (e.g. family history, cancer history, pathology results, genetic test results, and results of investigations such as colonoscopies). Encourage your patient to collect this information, if you do not have it, to facilitate a productive genetic counselling session and to prevent unnecessary delays when further clarification is needed before an appointment can be booked.

HOW WILL GENETIC TESTING HELP YOU AND YOUR PATIENT?

If a mutation is identified (a positive test result):

- Clinical intervention can improve outcomes.[17,18] (See Screening and Management for more)
  - Risk-reducing mastectomy lessens the risk of breast cancer by at least 90%
  - Annual magnetic resonance imaging plus mammography increases detection rate for breast cancer
  - Risk-reducing salpingo-oophorectomy decreases the risk of ovarian cancer by at least 80% and, if performed prior to menopause, can reduce the risk of breast cancer by at least 50%
  - Chemoprevention, e.g. tamoxifen, may be considered for some women as a risk-reducing option.
- Other at-risk family members can be identified and given accurate risk assessments[19]
- Positive health behaviours can be reinforced[19]

If a mutation is <u>not</u> identified and testing was for a <u>known familial mutation</u> (true negative):

- Your patient is not considered to be at increased risk of developing hereditary cancer but may still be at increased risk of cancer depending on family history
- You can provide reassurance to your patient and her/his children

ARE THERE HARMS OR LIMITATIONS OF GENETIC TESTING?

If a mutation is identified (a positive test result)[19]:

- Your patient may experience psychological distress knowing s/he is at increased risk to develop cancer, and/or over the possibility s/he may have passed the mutation to her/his children
- Family issues such as confidentiality concerns may inhibit the transfer of information between relatives
- Your patient may face insurance (life, disability, long-term) or job discrimination, although the increased risk over and above that associated with a strong family history of cancer may be small

- Incomplete penetrance – being identified as having a mutation does not mean one will develop cancer

If a mutation is not identified in an unaffected patient and testing was for a known familial mutation (true negative)[19,20]:

- Depending on family dynamics (some siblings may have tested positive while some have not) or extensive family history of cancer, your patient may experience psychological distress such as 'survivor guilt' or 'identity loss'
- Your patient may develop a complacent attitude to health and screening

If no mutation is identified in an affected patient who has no known familial mutation (uninformative result) or when a variant of uncertain significance (VUS) is identified[19]:

- The diagnosis of HBOC is neither confirmed nor ruled out, even in families with a strong history of breast and/or ovarian cancer
- Screening recommendations will be based on a combination of factors, such as family history and, in cases where a VUS was identified, information about the VUS
- Please consult your patient's specialist, also see Screening and Management

SCREENING AND MANAGEMENT

Breast Cancer: Screening recommendations for **high risk women** *(carriers of a mutation in BRCA1 or BRCA2 gene and their first degree relatives who have not yet had genetic testing)* vary according to provincial guidelines and access to imaging technologies. The literature demonstrates life expectancy gains with the use of breast MRI in addition to digital mammography[22]. The age at which to begin screening varies but generally is between 25 and 30 years[4,21,22]. For details about screening provincial/territorial breast cancer recommendations see Table 2 or consult your local hereditary cancer program for details about high risk screening.

Generally, breast awareness should be encouraged, starting at age 18, and breast changes should be reported to primary care providers.

Table 2. Canadian breast cancer screening programs.

Province/Territory	High risk breast cancer screening guidelines	Breast cancer screening program	Administrative agency
British Columbia	High risk eligibility	Breast cancer screening policy	BC Cancer Agency
Alberta	Recommendation for high risk populations High Risk Breast Cancer Clinic	Breast cancer screening resources for healthcare providers	Screeningforlife.ca – Alberta Health Services

Saskatchewan		Saskatchewan Screening Program for Breast Cancer (SPBC)	Saskatchewan Cancer Agency
Manitoba	Winnipeg Regional Health Authority (WRHA) Breast Health Centre	BreastCheck BreastCheck guidelines	Cancer Care Manitoba
Ontario	Ontario Breast Screening Program (OBSP) for high risk women	Ontario Breast Screening Program (OBSP) for average risk women	Cancer Care Ontario
Quebec		Québec Breast Cancer Screening Program | Le Programme québécois de dépistage du cancer du sein (PQDCS)	Santé et Services Sociaux Québec
New Brunswick		New Brunswick Breast Cancer Screening Program	New Brunswick Cancer Network (NBCN) is a branch of the Department of Health
Nova Scotia	Breast MRI Guidelines including high risk eligibility	Nova Scotia Breast Screening Program	Nova Scotia Department of Health and Wellness
Prince Edward Island		PEI Provincial Breast Screening Program	Health PEI
Newfoundland and Labrador	Breast Magnetic Resonance Imaging (MRI) and High Risk Hereditary Breast Cancer (SUMMARY,PDF, November 2012) Breast Magnetic Resonance Imaging (MRI) and High Risk Hereditary Breast Cancer (GUIDELINE, PDF, November 2012)	Breast Screening Program: Eastern Health Central Health Western Health	Cancer Care a program of Eastern Health

Yukon	Yukon Mammography Program at Whitehorse General Hospital	Yukon Hospital Corporation
Northwest Territories	NWT Breast Cancer Screening	NWT Health and Social Services
Nunavut		*Guidelines under review*

NOTE: Currently there are five provinces (British Columbia, Alberta, Ontario, Nova Scotia, Newfoundland and Labrador) that have developed standard guidelines for MRI referral.

High risk men: There are limited data on the use of imaging in men. Breast awareness should be encouraged.

Ovarian cancer: Screening for ovarian cancer has limited evidence of utility. Risk-reducing surgery, bilateral salpingo-oophorectomy (BSO), is recommended for women who have completed childbearing[4,21]. Women who elect not to have prophylactic BSO may be screened by pelvic examination, transvaginal ultrasound and CA-125 serum tumour marker every 6-12 months starting at age 30 or 5-10 years before the earliest diagnosis of ovarian cancer in the family[4,21]. Women should be counselled about the limitations of these screening techniques as they have not been shown to be effective strategies for cancer detection[4].

Prostate cancer: Screening according to provincial guidelines (e.g. annual digital rectal examination +/- prostate specific antigen), should begin at age 40[4,21].

Other BRCA related cancers: There are no specific screening guidelines for other *BRCA*-related cancers (e.g. pancreatic cancer, melanoma). Depending on the family history, an individualized screening plan may be considered. *BRCA1* and *BRCA2* mutation carriers should be educated about signs and symptoms of cancer(s). [4,21]

Risk-reducing interventions:

Women with no current or past diagnosis of breast cancer and who have a life expectancy of greater than 10 years can be counselled by their multidisciplinary healthcare teams about options for reducing lifetime risk of *BRCA1* and *BRCA2* related cancers.

Lifestyle modifications

Individuals should be encouraged to maintain a healthy lifestyle with proper diet, healthy BMI, regular exercise and limited alcohol consumption, in addition to staying up-to-date on current screening recommendations.

Risk-reducing surgery

Bilateral total mastectomy provides a high degree of protection against breast cancer (at least 90% reduction) in *BRCA1* and *BRCA2* mutation carriers[4,21]. *BRCA1* and *BRCA2* mutation carriers also have an increased lifetime risk of ovarian cancer and, in the absence of reliable early detection and the poor prognosis of ovarian cancer, *bilateral salpingo-oophorectomy (BSO)* can be offered to these women after completion of childbearing[34,21]. BSO has been shown to reduce the risk of ovarian cancer by about 80% in

BRCA1 and *BRCA2* mutation carriers[4,21]. If BSO is performed prior to menopause, a woman's breast cancer risk can also be reduced by about 50%, likely because of decreased hormonal exposure[4,21]. The residual risk for primary peritoneal carcinoma is estimated to be 1-4%[4,21].

Chemoprevention

The data are limited with regards to effectiveness of chemoprevention in *BRCA1* and *BRCA2* mutation carriers. The selective estrogen receptor modulator (SERM), Tamoxifen, has been shown to decrease the risk of contra-lateral breast cancer in *BRCA1* and *BRCA2* mutation carriers by at least 50%[4,21]. Limited data have shown that Tamoxifen can reduce breast cancer risk by about 62% in healthy *BRCA2* mutation carriers, who have a greater likelihood of developing ER-positive tumours, but with no effect on *BRCA1* mutation carrier breast cancer risk. There are insufficient data to recommend use of Tamoxifen in women under 35 years.

The results of various studies looking at the effect of the oral contraceptive pill (OCP) on increased breast cancer risk, particularly for *BRCA1* and *BRCA2* mutation carriers are not consistent. Overall, the risk for breast cancer associated with OCP does not seem to be greater for high-risk women (e.g. *BRCA1* and *BRCA2* mutation carriers) than for average risk women. The literature does show that OCP decreases the risk for ovarian cancer in average and in high risk women (a greater effect for *BRCA1* than *BRCA2* mutation carriers) and could be considered for some pre-menopausal women who have not yet completed childbearing.[23]

See www.geneticseducation.ca for the more concise version, GECKO on the run, and for a point of care tool. For general guidelines on HBOC management contact your local genetics centre.

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Authors: S Morrison MS CGC, C Cremin MS CGC, E Tomiak MD FRCPC, JE Allanson MD FRCPC and JC Carroll MD CCFP