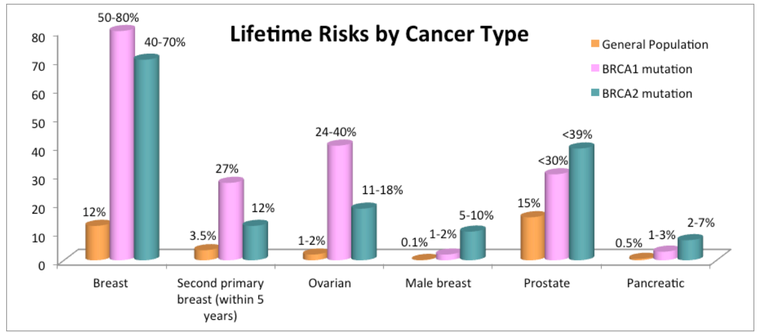
ASSOCIATED LIFETIME CANCER RISKS



Note: BRCA1/2 mutations can also increase the risk of developing other types of cancer including fallopian tube cancer, primary peritoneal cancer and melanoma.

SURVEILLANCE AND MANAGEMENT RECOMMENDATIONS

Specific recommendations will be made according to the gene-specific associated risk (BRCA1 or BRCA2). In general, current recommendations and options include:

For women with a BRCA1/2 mutation:	For men with a BRCA1/2 mutation:
Enhanced screening • Breast awareness, including self-breast exam • Routine clinical breast exam • Annual breast MRI and mammogram • Consider transvaginal ultrasound and CA-125 blood screen • Consider full body skin exam • Consider pancreatic cancer screening Prophylactic surgery • Bilateral mastectomy • Bilateral salpingo-oophorectomy Chemoprevention • Tamoxifen, oral contraceptives	Enhanced screening • Breast awareness, including self-breast exam • Routine clinical breast exam • Consider mammogram • Routine prostate cancer screening • Consider full body skin exam • Consider pancreatic cancer screening

For individuals with no mutation identified:
Cancer screening and prevention options should be based on their personal and family medical history.

LifeLabs Genetics™

REFERENCES

1. ACOG Committee on Practice Bulletins. Hereditary breast and ovarian cancer syndrome. Gynecol Oncol. 2009;113:6-11.
2. Alsop, K. et al., BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: A report from the Australian Ovarian Cancer Study Group. J Clin Oncol. 2012;30(21):2654-2663.
3. Anglian Breast Cancer Study Group. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Br J Cancer. 2000;83:1301-8.
4. Antoniou AC et al., Predicting the likelihood of carrying a BRCA1 or BRCA2 mutation: validation of BOADICEA, BRCAPRO, IBIS, Myriad and the Manchester scoring system using data from UK genetics clinics. J Med Genet. 2008a;45:425-31
5. ASHG. Statement of the American Society of Human Genetics on genetic testing for breast and ovarian cancer predisposition. Am J Hum Genet. 1994;55:i-iv.
6. Efrat G.K. et al., Population-based screening for breast and ovarian cancer risk due to BRCA1 and BRCA2. Proc Natl Acad Sci, 2014;111(39):14205-14210
7. Ghadirian, P. et al., The contribution of founder mutations to early onset breast cancer in French-Canadian women. Clin Genet. 2009;76(5):421-426.
8. Hampel H. et al., 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. Genet Med, 2015;17(1): 70-87
9. King MC, Marks JH, Mandell JB., New York Breast Cancer Study Group. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science.2003;302:643-6.
10. Lancaster JM et al., Society of Gynecologic Oncologists Education Committee. Society of Gynecologic Oncologists Education Committee statement on risk assessment for inherited gynecologic cancer predispositions. Gynecol Oncol. 2007 Nov;107:159-62.
11. Levy-Lahad E et al., A single nucleotide polymorphism in the RAD51 gene modifies cancer risk in BRCA2 but not BRCA1 carriers. Proc Natl Acad Sci U S A. 2001;98:3232-6.
12. NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast and Ovarian, http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
13. Oddoux C et al.,The carrier frequency of the BRCA2 6174delT mutation among Ashkenazi Jewish individuals is approximately 1%. Nat Genet. 1996;14:188-90.
14. Schrader, K. A. et al., Germline BRCA1 and BRCA2 mutations in ovarian cancer: utility of a histology-based referral strategy. Obst & Gynecol, 2012;120(2, Part 1):235-240.
15. Struewing JP et al., The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med. 1997;336:1401-8.
16. Tonin, P. N. et al., Founder BRCA1 and BRCA2 mutations in early-onset French Canadian breast cancer cases unselected for family history. Int J Cancer, 2001;95(3):189- 193.
17. US Preventive Services Task Force. Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: recommendation statement. Ann Intern Med.2005;143:355-61
18. Walsh, T. et al., Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proc Natl Acad Sci, 2011;108(44):18032-18037
19. Whittemore AS et al., Prevalence of BRCA1 mutation carriers among U.S.non-Hispanic Whites.Cancer Epidemiol Biomarkers Prev.2004b;13:2078-83.

RESOURCES

Genetics professionals such as medical geneticists and genetic counsellors can discuss conditions like HBOC in more detail and answer any questions you may have about genetic results. To find a genetics clinic near you visit the Canadian Association of Genetic Counsellors website www.cagc-accg.ca.

There are many online resources for individuals and families coping with the diagnosis and management of HBOC, some of which are listed below.

Hereditary Breast and Ovarian Cancer Society: **http://hbocsociety.org/**
Ovarian Cancer Canada: **http://www.ovariancanada.org/**
Willow : Breast and Hereditary Cancer Support: **http://www.willow.org/**
HBOC on GeneReviews: **http://www.ncbi.nlm.nih.gov/books/NBK1247/**
Canadian Cancer Society: **http://www.cancer.ca/**

The Field Of Genetics Is Always Evolving And So Are We Please Visit Our Website For A Current Test List

Ask.Genetics@LifeLabs.com www.lifelabsgenetics.com 1-844-363-4357

V.1 | JAN 2016 DETAIL AID

Hereditary Breast and Ovarian Cancer (HBOC): BRCA1 and BRCA2 genes

LifeLabs Genetics™ | CENTOGENE THE RARE DISEASE COMPANY

Ask.Genetics@LifeLabs.com www.lifelabsgenetics.com 1-844-363-4357

In the general population, about 12% of women (1 in 8) will develop breast cancer and about 1.3% (1 in 70) will develop ovarian cancer in their lifetime. While most of these cancers are not hereditary, 5-10% of breast cancer cases and around 15% of ovarian cancer cases are associated with a mutation in a cancer predisposition gene.

WHAT YOU NEED TO KNOW

Hereditary breast and ovarian cancer (HBOC) resulting from a mutation of BRCA1 or BRCA2 (BRCA1/2) is the most common form of both hereditary breast and ovarian cancers and occurs in all ethnic and racial populations. Both men and women can be carriers of a disease-causing BRCA mutation.

It is estimated that in the general population:
- 1/400 to 1/800 people carry a BRCA1/2 mutation.
- 1/40 individual of Ashkenazi Jewish ancestry carry a BRCA1/2 mutation.
- Increased carrier frequency for BRCA1/2 has been reported in the Dutch and Icelandic populations.

Recent publications have found that 20-50% of individuals with BRCA1/2 mutations have no reported family history of breast and/or ovarian cancer, with frequencies varying depending on patient ancestry and personal cancer history. Researchers have stated that family history alone may be an unreliable criterion for genetic testing decisions, especially in patients with ovarian cancer or of Ashkenazi Jewish ancestry.

Individuals with BRCA 1/2 mutations are more likely to develop cancer at a younger age and have high grade tumours. Among those who develop cancer, variable age of onset and type of cancer is observed, even within the same family.

BRCA1/2 mutations can also increase the risk of developing other types of cancer including fallopian tube or primary peritoneal cancer, male breast cancer, prostate cancer, pancreatic cancer and melanoma.

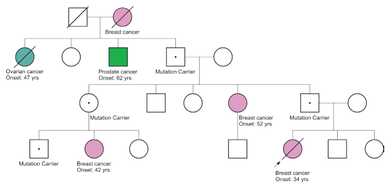
Other genes, although less frequent, are also associated with an increased risk of breast and ovarian cancer. LifeLabs Genetics offers genetic testing for most of these as well as multi-gene cancer panels. For more information about the genetic tests offered by LifeLabs Genetics, please visit our website at www.LifeLabsGenetics.com. You may also contact us by phone **Tel: 1-84-GENE-HELP | (1-844-363-4357) | email Ask.Genetics@lifelabs.com**

GENETICS

BRCA1 and BRCA2 mutations are inherited in an autosomal dominant manner.
- Each offspring of an individual with a BRCA1/2 mutation has a 50% chance of inheriting the mutation.

Most individuals with a BRCA1/2 mutation have inherited it from a parent.
- Each sibling of an individual with a BRCA1/2 mutation has a 50% chance of carrying the same mutation

Incomplete penetrance.
- Not all individuals with a cancer-predisposing mutation will develop cancer.



1/400 to 1/800 people carry a BRCA1 or BRCA2 mutation

CLINICAL INDICATIONS FOR GENETIC TESTING

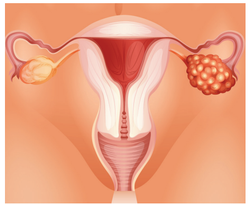
Based on current professional society guidelines, genetic testing for BRCA1 and BRCA2 is indicated for individuals with a personal and/or family history of any of the following:

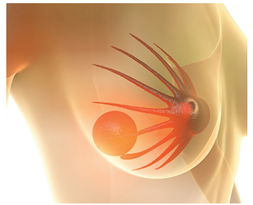
- Breast cancer diagnosed at age 50 or younger
- Multiple primary breast cancers either in the same breast or opposite breast
- Triple-negative breast cancer at age 60 or younger (ER-, PR- and HER2/neu -)
- Ovarian cancer, fallopian tube or primary peritoneal cancer at any age
- Both breast and ovarian cancer
- Male breast cancer at any age
- Pancreatic cancer with breast or ovarian cancer in the same individual or on the same side of the family
- Two or more relatives with breast cancer, one under age 50
- Three or more relatives with breast, ovarian, pancreatic, and/or aggressive prostate cancer
- Ashkenazi Jewish ancestry with history of breast, ovarian or pancreatic cancer
- A previously identified BRCA1 or BRCA2 pathogenic mutation in the family

*Limited family history may not allow for evaluation of these criteria.

Note that publicly-funded hereditary cancer programs in Canada may use more restrictive criteria when selecting patients for HBOC genetic testing. Therefore, not all patients will be eligible for testing through these clinics.

Whenever possible, genetic testing should be performed on a family member diagnosed with either breast or ovarian cancer. If the affected family member is deceased or is not willing or able to participate in genetic testing, testing may be performed on individuals without a cancer diagnosis with the understanding that failure to detect a pathogenic mutation does not eliminate the possibility of a BRCA1 or BRCA2 mutation being present in the family.





GENETIC COUNSELLING

A cancer genetic consultation is an important aspect of care for individuals with risk factors associated with a hereditary cancer syndrome. Pre-test counselling is recommended for individuals concerned about their possible risks of HBOC and/or considering genetic testing.

A pre-test session usually includes:
- A hereditary cancer risk assessment based on personal and family medical history.
- Discussion of the appropriateness of genetic testing.
- Medical and psychological implications of test results.
- Possibility of an uninformative result.
- Risk to other family members.

Post-test genetic counselling is also recommended to understand the implications of the results.

BENEFITS OF TESTING

Genetic testing can provide individuals and their families with important information by:
- Confirming a genetic aetiology to a cancer diagnosis.
- Guiding surveillance, prevention and management decisions.
- Clarifying risks to family members.
- Empowering individuals to make family planning decisions.

Lifelabs Genetics offers various types of genetic testing to answer each specific clinical situation. These methods include Sanger Sequencing, MLPA (for deletion/duplication), Next Generation Sequencing (NGS) for multi-gene panels and direct mutation testing for known familial mutations.

Genetic testing can seem complicated. Our team of certified genetic counsellors and client-care specialists are available to support you along the way.

POSSIBLE RESULTS

Positive
- A disease-causing mutation was identified.
- This individual has an increased risk for specific types of cancer.
- Family members are at increased risk of carrying the same mutation.

True Negative
- This individual tested negative for a mutation previously identified in the family.
- This individual's risk for cancer is not expected to be increased above the general population risk.

Uninformative negative

Individual with a cancer diagnosis.
- No disease-causing mutation was identified.
- Could not identify a genetic aetiology for the diagnosis.
- Additional genetic testing may be considered based on medical and family history.

Individual without personal history of cancer.
- No disease-causing mutation was identified.
- The exact cause of the cancers in the family remains unknown.
- This individual's risk for cancer remains increased based on family history assessment.
- When possible, testing affected family members should be considered.

Variant of Unknown Significance (VUS)
- A VUS indicates that the pathogenicity of the variant identified cannot be established.
- Testing other family members may help clarify the clinical significance.
- Over time, variants may be reclassified as pathogenic or non-pathogenic.

15% of all ovarian cases are hereditary

5-10% of all breast cancer cases are hereditary