Mount Sinai Hospital
Sinai Health System
Joseph & Wolf Lebovic Health Complex

Family & Community Medicine
UNIVERSITY OF TORONTO

CanImpact®
Improving Cancer Care Together

Personalized Cancer Genomic Medicine Resource Toolkit

ONTARIO

March 2016

The CanIMPACT Personalized Cancer Genomic Medicine Research Team:

June C. Carroll MD CCFP FCFP [1, 2] – Principal Investigator
Elizabeth A. Eisenhauer MD FRCPC FRSC [3, 4] – Co-Principal Investigator
Julie Easley PhD[5]
Eva Grunfeld MD DPhil CCFP FCFP [2, 6]
Ruth Heisey BSc MD CCFP FCFP [2, 7]
Monika Krzyzanowska MD MPH FRCPC [8, 9, 10]
Tutsirai Makuwaza MA [1, 2]
Donna Manca MD MClSc CCFP [11]
Baukje Miedema PhD [5, 12]
Mary Ann O'Brien MSc PhD [2]
Joanne A. Permaul MA CCRP [1]
Sandhya Pruthi MD [13]
Carol Sawka MD [9]
Nancy Schneider [14]
Nicolette Sopcak PhD [11]
Jonathan Sussman MD MSc CCFP FRCPC [15]
Robin Urquhart PhD [12, 16]
Catarina Versaevel [11]

[1] Ray D. Wolfe Department of Family Medicine, Sinai Health System, Toronto
[2] Department of Family & Community Medicine, University of Toronto
[3] Department of Oncology, Kingston General Hospital
[4] Department of Oncology, Queen's University
[5] Department of Family Medicine, Dalhousie University
[6] Ontario Institute for Cancer Research, Toronto
[7] Department of Family & Community Medicine, Women's College Hospital, Toronto
[8] Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto
[9] Institute of Health Policy, Management and Evaluation, University of Toronto
[10] Cancer Care Ontario
[11] Department of Family Medicine, University of Alberta
[12] Beatrice Hunter Cancer Research Institute
[13] General Internal Medicine, Mayo Clinic, Rochester, Minnesota
[14] Independent
[15] Department of Oncology, McMaster University
[16] Department of Surgery, Dalhousie University

CIHR IRSC
Canadian Institutes of Health Research | Instituts de recherche en santé du Canada

This study was supported by the Canadian Institutes of Health Research www.cihr-irsc.gc.ca

Personalized Cancer Genomic Medicine
Resource Toolkit - ONTARIO

Table of Contents

Red Flags to Identify Individuals Who Are at Increased Risk of a Hereditary Cancer Syndrome

In general, suspicion of a hereditary cancer syndrome should be raised if:

- There are multiple family members with cancer
- 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)
- Clustering of certain types of cancers is present
- Multiple primary cancers are diagnosed in same individual

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.

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. 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*).

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. Founder mutations are observed in individuals of Ashkenazi Jewish ethnicity occurring at an estimated frequency of about 1 in 50.

WHO SHOULD BE OFFERED REFERRAL TO GENETICS AND POSSIBLE GENETIC TESTIING?

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:

- 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, 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.

See the *GEC-KO point of care tool* which can be used in your practice to help identify patients that would benefit from referral to genetics or your local hereditary cancer program.

HOW WILL GENETIC TESTING HELP YOU AND YOUR PATIENT?

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

- Clinical intervention can improve outcomes. (See *GECKO Messenger for Screening and Management)
  - 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
- Positive health behaviours can be reinforced

- *If a mutation is not identified and testing was for a known familial mutation (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 their children

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*	
Cumulative lifetime invasive **breast cancer risk in women** (by age 70)	57%	49%	~12%
Cumulative lifetime **ovarian cancer risk (**by age 70)	40%	18%	~1.3%
Cumulative lifetime **breast cancer risk in men** (by age 70)	Increased (*controversial*)	6-7%	0.1%
Lifetime **prostate cancer risk** (by age 70)	n/a	2-6x increased risk	~14%

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.

For a recent review article on HBOC see Moyer VA, U.S. Preventive Services Task Force. Risk assessment, genetic counselling, and genetic testing for BRCA-related cancer in women: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2014; 160(4):271-81.

See www.geneticseducation.ca for the comprehensive *GEC-KO Messenger* with references and more on risks, benefits, limitations, screening and management, as well as for the made for practice*point of care tool.*

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

Part I: Hereditary breast and ovarian cancer screening tool to identify patients most likely to benefit from referral to genetics

Part I of this tool is to be used with patients to predict who should be referred for genetic counselling due to increased risk for a hereditary breast cancer syndrome including but not limited to hereditary breast and ovarian cancer (HBOC) syndrome caused by mutations in *BRCA1* and *BRCA2* genes. Part II of this tool is used to identify individuals who are at high risk to carry a mutation in *BRCA1* or *BRCA2* genes.

1. Did any of your first degree relatives (parent, sibling, child) have breast *or* ovarian cancer?	Yes ❒	No ❒
2. Did any of your relatives have bilateral breast cancer?	Yes ❒	No ❒
3. Did any man in your family have breast cancer?	Yes ❒	No ❒
4. Did any woman in your family have breast *and* ovarian cancer?	Yes ❒	No ❒
5. Did any woman in your family have breast cancer before the age of 50 years?	Yes ❒	No ❒
6. Do you have 2 or more relatives with breast *and/or* ovarian cancer?	Yes ❒	No ❒
7. Do you have 2 or more relatives with breast *and/or* bowel cancer?	Yes ❒	No ❒

Management: **With 1 or more** positive responses, discuss referral to genetics

This POC tool is based on the Family History Screening-7 (FHS-7) (Ashton-Prolla *et al* 2009), which was designed for use in primary care settings and demonstrated an overall sensitivity of 97.0% and a specificity of 53.0% for HBOC syndrome. Overall, **using as cut point one positive answer**, the sensitivity and specificity of the instrument were 87.6% and 56.4%, respectively for hereditary breast cancer syndromes.

(Reference: Ashton-Prolla P, Giacomazzi J, Schmidt AV, *et al*. Development and validation of a simple questionnaire for the identification of hereditary breast cancer in primary care. *BMC Cancer* 2009; 9:283

On-line tool: Breast Cancer Genetics Referral Screening Tool (B-RST™)

This is an on-line screening tool for health care providers and the general public to enter family history information to determine who should be referred for cancer genetic counselling for Hereditary Breast and Ovarian Cancer. www.breastcancergenescreen.org

CanImpact Improving Cancer Care Together

GEC•KO Genetics Education Canada • Knowledge Organization

Part II: Red Flags to identify patients at **high risk** of hereditary breast and ovarian cancer most likely to benefit from referral to genetics

(TAKEN DIRECTLY from GECKO On the Run on Hereditary Breast/Ovarian Cancer)

These are general guidelines to identify patients at **high risk** for hereditary breast and ovarian cancer (HBOC) syndrome. 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:

- 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 (e.g., 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, 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. three common mutations in those of Ashkenazi Jewish ethnicity). A negative result in this situation only rules out those ethnic-specific mutations.

For more information on Hereditary Breast and Ovarian Cancer such as screening recommendations and references see the complete *GEC-KO Messenger* at www.geneticseducation.ca

OBSP Requisition for High Risk Screening

1. Client Information (*or affix label*)	
First name	Last name
Date of birth (dd/mmm/yyyy)	OHIP number
Telephone number Secondary telephone number	Address (*including postal code*)

To receive high risk breast screening (*i.e.: annual MRI and mammogram*), women must be **between 30 and 69 and** be at high risk for breast cancer as identified through **Category A OR Category B**, after genetic assessment. **Women with bilateral mastectomies are not eligible**.

Category A: eligible for **direct entry** into the program. To fall under this category, **at least one** of the following criteria must be met:

- ☐ Known carrier of a gene mutation (*e.g. BRCA1, BRCA2* - ***fax results with form***)
- ☐ First degree relative of a carrier of a gene mutation (*e.g. BRCA1, BRCA2*), has previously **had** genetic counselling, and has **declined** genetic testing
- ☐ Previously assessed as having a ≥25% lifetime risk of breast cancer on basis of family history (*a genetic clinic must have used **at least one** of the tools below to complete this assessment* – ***fax results with form***)
  - *IBIS 10 Year Risk:* *BOADICEA 5 Year Risk:*
  - *IBIS Lifetime Risk:* *BOADICEA Lifetime Risk:*
- ☐ Received chest radiation (not chest x-ray) before age 30 and at least 8 years previously (*e.g. as treatment for Hodgkin's Lymphoma*)

OR

Category B: genetic assessment required (*i.e. counselling and/or testing*) to determine eligibility for the program. To fall under this category, **at least one** of the following criteria must be met:

- ☐ First degree relative of a carrier of a gene mutation (*e.g. BRCA1, BRCA2*) and has **not** had genetic counselling or testing
- ☐ A personal or family history of **at least one** of the following (*please check all that apply*):
  - ☐ Two or more cases of breast cancer and/or ovarian* cancer in closely related blood relatives†
  - ☐ Bilateral breast cancers
  - ☐ Both breast and ovarian* cancer in the same woman
  - ☐ Breast cancer at ≤35 years of age
  - ☐ Invasive serous* ovarian cancer
  - ☐ Breast and/or ovarian* cancer in Ashkenazi Jewish families
  - ☐ An identified gene mutation (*e.g. BRCA1, BRCA2*) in any blood relatives
  - ☐ Male breast cancer

** Includes cancer of the fallopian tubes and primary peritoneal cancer*
† Closely related blood relative: 1st degree = parent, sibling, or child; 2nd degree = grandparent, aunt, uncle, niece, or nephew

2. Clinical History	
Date and location of most recent mammogram	Previous breast cancer? ◯ Yes ◯ No
Date and location of most recent MRI (*if done*)	Breast implants? ◯ Yes ◯ No
Previous genetic assessment for inherited breast cancer risk? ◯ Yes (***attach results***) ◯ No	Specify genetic assessment centre

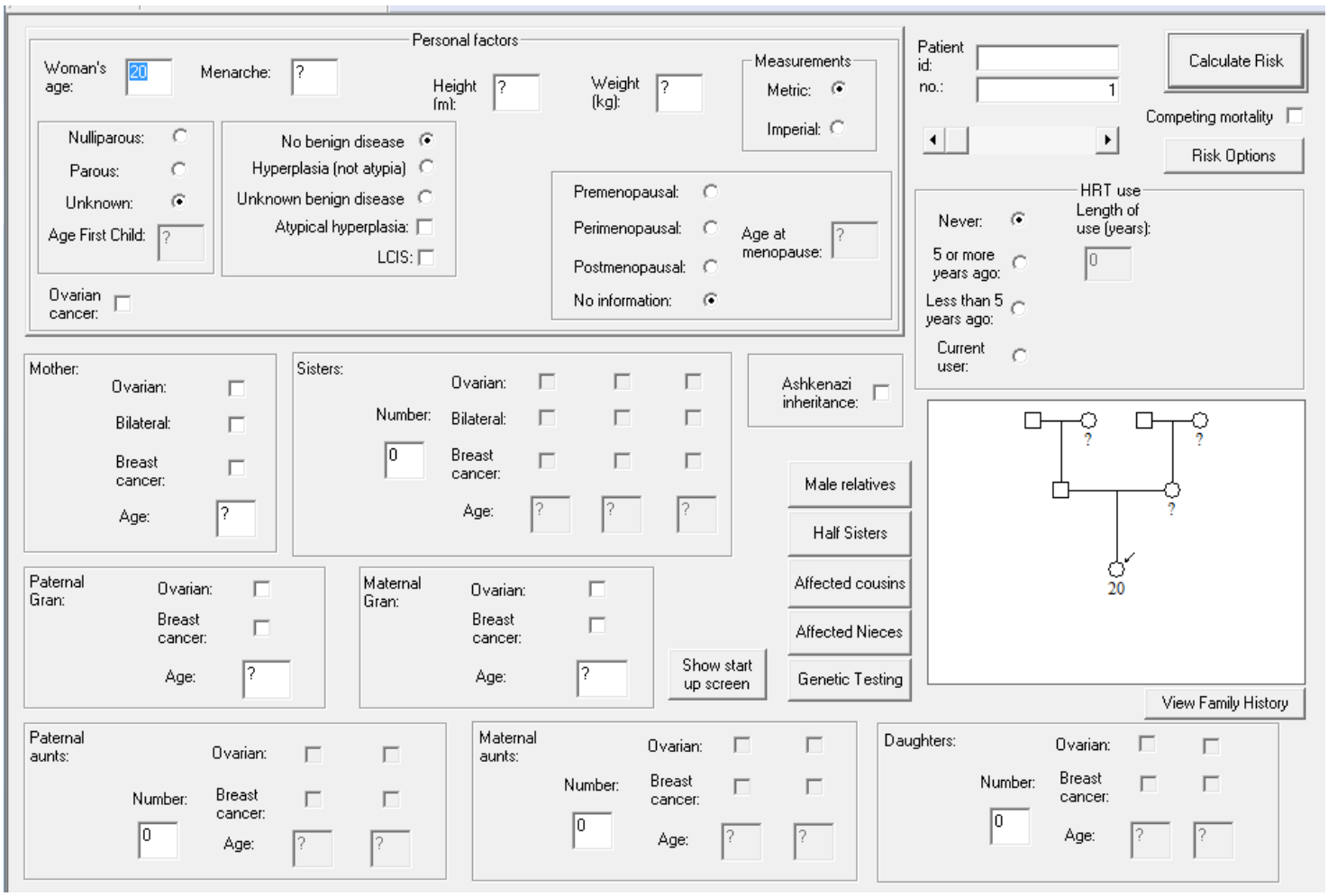
3. Referring Physician	
First and last name	CPSO Number
Address (*including postal code*)	Telephone number
Signature Date (dd/mmm/yyyy)	Fax number

By signing this form, you authorize your client to receive screening mammography and MRI (or, if appropriate, screening ultrasound). You also authorize the OBSP to book these screens, additional screens, as well as any follow-up appointments, including imaging tests and biopsies for evaluation of abnormal results. **Fax completed form to the OBSP High Risk Screening Referral Contact in your area (cancercare.on.ca/obsphighrisk)**.

IBIS Breast Cancer Risk Evaluation Tool

- This tool is provided mainly for your information only as it is one of the tools used by the Ontario Breast Screening Program and by genetics clinics to calculate risk of breast cancer.
- This tool can be completed on-line to calculate the numeric likelihood of breast cancer (lifetime and 10-year cancer risk) and the likelihood of carrying an adverse gene mutation, which would affect a patient's likelihood of developing breast cancer.
- The patient's personal details, family history and some clinical details are entered then the risk is calculated.
- At present, this program is only compatible with PC, not MAC users.
- http://www.ems-trials.org/riskevaluator/

Evaluation Screen of IBIS Tool



CanImpact®
Improving Cancer Care Together

Chemoprevention for Breast Cancer

The purpose of this tool is to raise your awareness about the potential benefits of chemoprevention in high risk women, particularly mutation carriers.

Red Flags to identify patients most likely to benefit from chemoprevention for breast cancer

Consider referring your patient to a breast clinic/familial oncology clinic for discussion of chemoprevention if she meets **any** of the following criteria (Grade B recommendation[+]):

1. Has a personal history of atypical hyperplasia or lobular carcinoma in situ on breast biopsy ☐ YES ☐ NO

2. Has a 5 year risk* of breast cancer ≥ 3% or a lifetime risk** of breast cancer ≥25% ☐ YES ☐ NO

3. Is less than age 50 with a strong family history of breast cancer (two first degree relatives with a history of breast cancer or one first degree relative with cancer onset <50 years of age) ☐ YES ☐ NO

4. Had therapeutic chest wall radiation when she was less than age 30 and at least 8 years previously (e.g. mantle radiation for Hodgkin's disease) ☐ YES ☐ NO

5. Is a genetic mutation carrier (*BRCA1, BRCA2, TP53, CDH1, CHEK2, PALB2*) ☐ YES ☐ NO

And

She is ≥ 35 years of age with no significant risk factors for blood clotting or endometrial cancer ☐ YES ☐ NO

*measured by the BRCAT (modified Gail risk calculator) www.cancer.gov/brisktool
** measured using the IBIS (http://www.ems-trials.org/riskevaluator/) risk calculator

[+] The US Preventive Services Task Force recommends this service. Grade B indicates that there is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial. Recommendation is that providers should engage in shared informed decision making and offer to prescribe risk-reducing medication if appropriate to asymptomatic women aged ≥35 years without a prior diagnosis of breast cancer who are at increased risk for the disease.

Treatment Options

NOTE: Chemoprevention only reduces the likelihood of estrogen receptor positive cancers

1. Tamoxifen at 20 mg per day for 5 years has been shown to reduce the incidence of breast cancer by 49% in women at increased risk for the disease. For those with a history of atypical hyperplasia an 86% reduction was seen. It is estimated that 22 women need to be treated for 5 years to prevent 1 breast cancer in the next 20 years. (Cuzick 2015)

Side effects include an increased risk of cataracts and hot flashes, thromboembolic disease (deep vein thrombosis and pulmonary embolus) (1.66 RR) and endometrial cancer/hyperplasia (1.64RR) in women over 50 years of age. It is estimated that 1 out of 167 women would have a thromboembolic event with 5 years of treatment. Age is a significant factor in determining impact or adverse effects. Women under the age of 50 do not appear to be at increased risk for endometrial cancer.(Cuzick 2015) Women of reproductive age should use contraception while on tamoxifen.

2. Raloxifene at 60 mg per day for 5 years is almost as effective as tamoxifen with a similar side effect profile, except it does not tend to cause endometrial hyperplasia/cancer. It may only be used in postmenopausal women and is “off label” as it is only approved in Canada for osteopenia/osteoporosis.

Any woman ≥35y with a 5-year risk of 1.7% or more qualifies for consideration of chemoprevention but those with a ≥3% risk have a more favorable benefit to risk profile.

Women most likely to benefit from chemoprevention are those less than age 50 and those with atypical hyperplasia.

Note: At this time both Tamoxifen and Raloxifene are not approved by Health Canada for the indication of chemoprevention so use would be “off-label”.

References:

The Guide to Clinical Preventive Services 2014. Agency for Healthcare Research and Quality (AHRQ) and U.S. Preventive Services Task Force

Cuzick J, Sestak I, Cawthorn S, Hamed H, Holli K, Howell A, Forbes JF on behalf of the IBIS-1 Investigators. Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-1 breast cancer prevention trial. Lancet Oncol 2015;16:67-75.

Cullen, K and Domino F. Can Tamoxifen Prevent Breast Cancer? Review Lancet Oncol 2015 Jan 16(1) 67-75.

Pruthi S, Heisey RE, Bevers TB. Chemoprevention for Breast Cancer. Ann Surg Oncol 2015.

Pruthi S, Heisey RE, Bevers TB. Personalized assessment and management of women at risk for breast cancer in North America. Womens Health 2015;11(2):213–224.

CanImpact®
Improving Cancer Care Together

Oncotype DX® testing in breast cancer

What is it?

Oncotype DX® is a specialized assay that evaluates the level of expression of a number of genes in breast cancer tissue that provides prognostic information useful in making decisions about adjuvant chemotherapy treatment.

When is it done?

This test is ordered by oncologists, and reimbursed by government, for women with breast cancer who meet the following criteria:

- Have newly diagnosed invasive breast cancer that is:
    - Axillary node negative OR only microscopically node positive
    - Estrogen receptor (ER) positive and HER2 negative
- Who are being offered adjuvant endocrine therapy (such as tamoxifen)

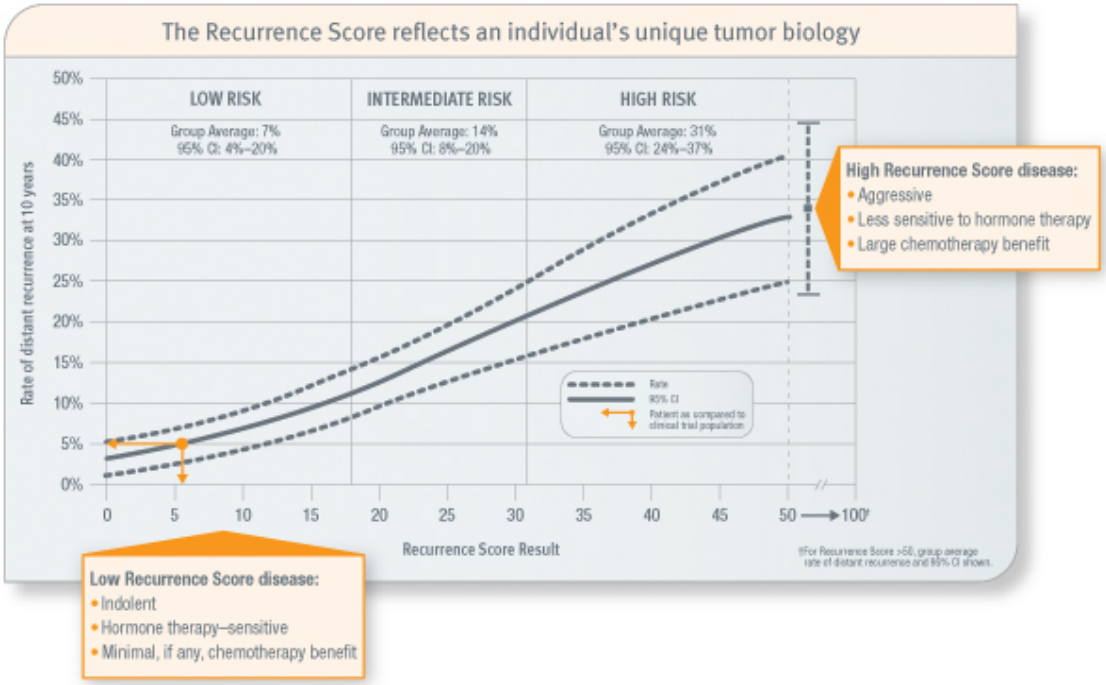
This group of patients has a *generally* good prognosis, **but** within this group, there is a subset of patients with a relatively high chance of recurrence that could benefit by the addition of adjuvant ***chemotherapy***. By evaluating expression of genes associated with recurrence, the Oncotype DX® test helps discriminate good and poor prognosis patients and this in turn helps in decision making around ***the benefit of adding adjuvant chemotherapy to adjuvant endocrine treatment.***

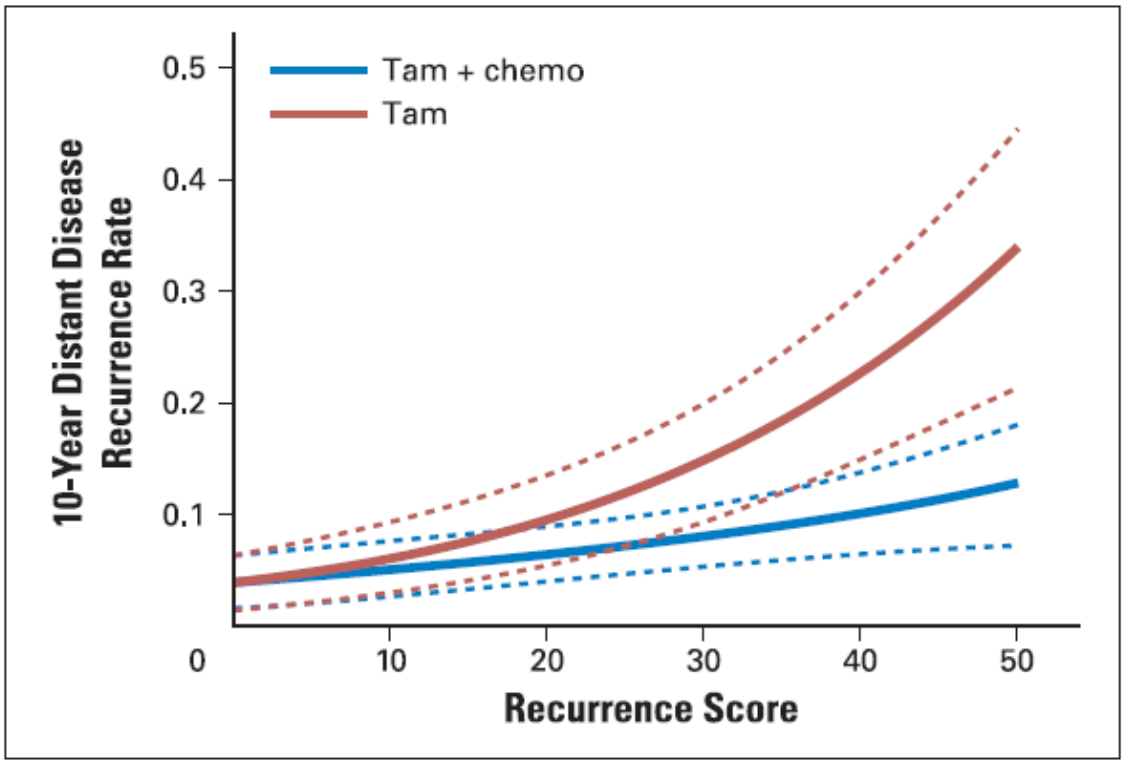
Oncotype DX® test results:

The "output" of the assay, which usually takes about 2-3 weeks to perform, is a "**recurrence score**" (see image below. The score will be a point on the solid line – the dotted lines are the confidence intervals around the value). The higher the score the greater the chance of recurrence and the more benefit adjuvant chemotherapy can offer. By corollary, a low score means a low chance of recurrence and little benefit from adding adjuvant chemotherapy.

The added benefit produced by chemotherapy when added to Tamoxifen is illustrated in the graph below. As can be seen between scores of 0 and 50, the added benefit of chemotherapy (**blue** line) over tamoxifen alone, (**red** line), increases - *so the benefit of adding chemotherapy in terms of reducing 10-year recurrence rates is greatest for patients whose tumours have the highest scores.*

These are complicated data for some patients to understand. The role of the family physician may be to help in the treatment decision making process– particularly for women in the "intermediate" score group where, depending on the patient's values and the risks she is willing to consider, some may choose to undergo chemotherapy and others will not. Patients must weigh the risks and absolute benefits of chemotherapy against potential gains for them.


The Recurrence Score reflects an individual's unique tumor biology
LOW RISK
Group Average: 7%
95% CI: 4%–20%
INTERMEDIATE RISK
Group Average: 14%
95% CI: 8%–20%
HIGH RISK
Group Average: 31%
95% CI: 24%–37%
Rate of distant recurrence at 10 years
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
0
5
10
15
20
25
30
35
40
45
50
100
Recurrence Score Result
High Recurrence Score disease:
• Aggressive
• Less sensitive to hormone therapy
• Large chemotherapy benefit
Low Recurrence Score disease:
• Indolent
• Hormone therapy–sensitive
• Minimal, if any, chemotherapy benefit


Tam + chemo
Tam
10-Year Distant Disease Recurrence Rate
0.5
0.4
0.3
0.2
0.1
0
10
20
30
40
50
Recurrence Score

LYNCH SYNDROME

Bottom line: Lynch syndrome (LS), also known as Hereditary Non-Polyposis Colorectal Cancer (HNPCC), is the most common hereditary colorectal (CRC) cancer predisposition syndrome. It is an autosomal dominant condition that causes a significant increased lifetime risk of CRC and endometrial (uterine) cancer in addition to other cancers. Individuals suspected of having LS should be referred for a genetic consultation for consideration of genetic testing. Screening, surveillance and management of CRC and other cancers should be guided by genetic test results and/or family/ personal history. Studies show that conversations between patients and their healthcare providers are the strongest driver of screening participation.

WHAT IS LYNCH SYNDROME?

Lynch syndrome (LS) is an autosomal dominant cancer predisposition syndrome caused by inherited mutations in genes responsible for correcting DNA replication errors, called mismatch repair (MMR) genes. **Individuals with LS have a high risk for colorectal and endometrial cancers** and a moderate risk for other cancers (Box 1 and Table 1). Not all individuals who inherit a mutation in a LS gene will develop cancer (*reduced penetrance*) and the signs and symptoms, type and age of onset of cancer will vary within families (*variable expressivity*).

BOX 1: LYNCH SYNDROME-RELATED CANCERS

✓ **Colorectal**	✓ **Endometrial**	✓ Kidney	✓ Gastric	✓ Ovarian	✓ Ureter	
✓ Small bowel	✓ Hepatobiliary	✓ Pancreatic				
✓ Brain	✓ Sebaceous (adenoma or carcinoma)					

PREVALENCE

LS accounts for about 0.7-3.6% of cases of CRC. Research on LS-related endometrial cancer is still emerging; current data suggest that in North America between 1.8% and 4.5% of cases are attributed to LS.

PERSONAL HISTORY RED FLAGS TO CONSIDER GENETIC TESTING OR GENETIC CONSULTATION

These are general guidelines to identify patients at **high risk** for LS. You should check with your local genetics centre or hereditary cancer program for more specific details. Consider referring your patient if he/she has:

- An early age of CRC diagnosis (<50 years). Patients diagnosed <35years are much more likely to have LS.
- An early age of endometrial cancer diagnosis (<50 years)
- Multiple primary LS-related cancer diagnoses, regardless of age
- A CRC diagnosis and one or more 1st degree relatives with a LS-related cancer, with one of the cancers being diagnosed <50 years
- A CRC diagnosis and two or more 1st or 2nd degree relatives with LS- related cancers regardless of age
- A CRC diagnosis <60 years with histological features suspicious for LS (excess infiltrating lymphocytes, mucinous/signet cell features, Crohn's-like reaction), particularly when primary tumour is right-sided

FAMILY HISTORY RED FLAGS TO CONSIDER GENETIC CONSULTATION

You should consider referring your patient to your local genetics centre or hereditary cancer program for further assessment if he/she is at **high risk** for hereditary CRC syndrome.

A patient is considered to be at **high risk** for LS syndrome if he/she

- Has a known LS causing mutation in the family

Or if he/she meets the revised Amsterdam criteria, meaning he/she:

- Has **at least three relatives** with a cancer associated with LS (Box 1); the following criteria should also be present:
  - One must be a first degree relative of the other two;
  - At least two successive generations must be affected (autosomal dominant inheritance);
  - At least one relative with LS-related cancer should be diagnosed before age 50;

  Tumours should be verified when possible and other CRC syndromes should be ruled out

If your patient does not have cancer, genetic testing of a relative with cancer may be recommended as a first step.

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 family members with cancer
- 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)
- Clustering of certain types of cancers is present (for LS, see Box 1)
- Multiple primary cancers are diagnosed in same individual

HOW IS GENETIC TESTING DONE?

Ideally testing begins with immunohistochemical (IHC) analysis of a CRC tumour for the proteins associated with the LS genes (*MLH1, MSH2, MSH6*, *PMS2* and *EPCAM*). IHC analysis looks at the protein products of the LS genes. If IHC analysis reveals a protein to be deficient, genetic testing can be offered to the affected individual and performed on a blood sample. If IHC analysis does not clearly show protein deficiency, the next step is often microsatellite instability (MSI) testing of the tumour sample. If MSI is stable or low, no further testing is indicated. If MSI is high, genetic testing can be offered to the affected individual and performed on a blood sample. Some centres will arrange IHC or MSI alone; others will carry out both tests at the same time.

WHAT DOES THE GENETIC TEST RESULT MEAN?

If your patient has been found to carry a mutation in a LS gene, **a positive result**, he/she has an increased lifetime risk to develop certain cancers (Table 1 and Box 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. These individuals may still have modified screening recommendations based on their family history. 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. In both of these cases, the diagnosis of LS is not confirmed or ruled out, especially in families with a strong history of CRC.

Table 1. Significant lifetime cancer risks for individuals who have inherited a mutation in the LS genes, *MLH1* and *MSH2*, as compared to the general population. *Risks for other LS genes are lower.*

Cancer type	**LS lifetime cancer risk in a carrier of a *MLH1* or *MSH2* gene mutation**		**General Population lifetime cancer risk < 70 years**
	Risk	Mean age of diagnosis	Risk
Colon	52-82%	44-61 years	5.5%
Endometrium	25-60%	48-62 years	2.7%

Screening and Surveillance

In general, for **high risk** individuals *(carriers of a mutation in a LS gene and their first degree relatives who have not yet had genetic testing) screening recommendations are as follows:*

Colorectal Cancer: Colonoscopy every 1-2 years beginning between ages 20 and 25 or 2-5 years prior to the earliest diagnosis *if* that diagnosis was made before age 25 years, whichever is earlier.

Endometrial and Ovarian cancer: Screening for endometrial or ovarian cancer may include annual transvaginal ultrasound and endometrial biopsy, however, there is little evidence of the effectiveness of these tests. Most importantly, women should be educated about the symptoms of endometrial cancer. Prophylactic hysterectomy and bilateral salpingo-oophorectomy is a risk-reducing option that LS women who have completed childbearing can consider.

Individuals who have tested negative for a known familial LS gene should follow provincial guidelines for population risk CRC screening, i.e. Fecal Occult Blood Test every two years from age 50. For those individuals who have a family history of CRC unrelated to the mutation in their family (i.e. on the other side of the family), screening recommendations would be based on the family history. Consult your local genetics centre or hereditary cancer program.

For individuals where no mutation was identified and there was no known familial mutation (*uninformative result*) **or** when a variant of uncertain significance (*VUS*) was identified, 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.

CRC screening for **intermediate risk** individuals is dependent on family history. For a person with a:

- 1st degree relative with CRC diagnosis <50 years or two 1st degree relatives with CRC at any age → Colonoscopy at age 40 or 10 years younger than the youngest CRC diagnosis, repeat 3-5 yearly
- 1st degree relative with CRC diagnosis ≥50 years → Colonoscopy at age 50 or 10 years younger than the youngest CRC diagnosis, repeat 5 yearly
- 2nd degree relative with CRC diagnosis <50 years → Colonoscopy at age 50, repeat dictated by findings

See www.geneticseducation.ca for the full GEC-KO *Messenger* on LS for more details. For general guidelines on CRC management: National Comprehensive Cancer Network (NCCN) Guidelines for colorectal cancer screening V.2.2013 [Login required – no fee]

Authors: S Morrison MS CGC, JE Allanson MD FRCPC, E Tomiak MD FRCPC, K Semotiuk MS (C)CGC and JC Carroll MD CCFP

Part I: Colorectal cancer risk assessment tool to identify patients most likely to benefit from referral to genetics

	YES	NO
1) Do you have a **first-degree relative** (mother, father, brother, sister, or child) with any of the following conditions diagnosed before age 50?		
Colon or rectal cancer _____	☐	☐
Cancer of the uterus, ovary, stomach, small intestine, urinary tract (kidney, ureter, bladder), bile ducts, pancreas, or brain _____	☐	☐
2) Have **you** had any of the following conditions diagnosed before age 50?		
Colon or rectal cancer _____	☐	☐
Colon or rectal polyps _____	☐	☐
3) Do you have three or more relatives with a history of colon or rectal cancer? (this includes parents, brothers, sister, children, grandparents, aunts, uncles, and cousins]) _____	☐	☐

The cumulative sensitivity of these three questions to identify patients with characteristics suggestive of hereditary colorectal and who should undergo a more extensive risk assessment is 77%. When all 3 questions were answered "yes", the tool correctly identified 95% of individuals with germline mutations causing Lynch syndrome. **If a patient answers "yes" to all of these questions a referral to genetics should be offered. If a patient answers "yes" to any of these questions, consider further assessment using the criteria in Part II.**

CanImpact Improving Cancer Care Together

GEC•KO Genetics Education Canada - Knowledge Organization

Part II: Red Flags to identify patients **at high risk** of **Lynch Syndrome** most likely to benefit from referral to genetics

Personal History LS Red Flags	Family History LS Red Flags

Consider referring your patient if he/she has:
• Colorectal cancer (CRC) diagnosis at an early age (<50 years). Higher suspicion of LS if diagnosed <35years.
• Endometrial cancer diagnosis at an early age (<50 years)
• Multiple primary LS-related cancer diagnoses, regardless of age
• A CRC diagnosis and one or more 1st degree relatives with a LS-related cancer, with one of the cancers diagnosed <50 years
• A CRC diagnosis and two or more 1st or 2nd degree relatives with LS- related cancers regardless of age
• A CRC diagnosis <60 years and histological features suspicious for LS*(excess infiltrating lymphocytes, mucinous/signet cell features, Crohn's-like reaction), particularly when primary tumour is right sided
	Consider referring your patient if he/she:
	• Has a known LS causing mutation in the family
	• Meets the revised Amsterdam criteria, meaning he/she has **at least three relatives** with a cancer associated with LS (Box 1). The following criteria should also be present:
	  • One must be a first degree relative of the other two;
	  • At least two successive generations must be affected (autosomal dominant inheritance);
	  • At least one relative with LS-related cancer should be diagnosed before age 50;
	Tumour pathology should be verified when possible and other CRC syndromes should be ruled out

**LS is the abbreviation for Lynch syndrome*

BOX 1: LYNCH SYNDROME-RELATED CANCERS

✓	**Colorectal**	✓	**Endometrial**	✓	Kidney	✓	Gastric	✓	Ovarian
✓	Small bowel	✓	Hepato-biliary	✓	Pancreatic	✓	Brain	✓	Sebaceous (adenoma or carcinoma)
✓	Ureter								

For more information on Lynch Syndrome such as screening recommendations see the complete GEC-KO Messenger at www.geneticseducation.ca

For information on a variety of genetics/genomics topics go to:

www.geneticseducation.ca

GECKO contains:

- Evidence based up-to-date resources on a variety of genomic topics ready to use at point of care
- Information on local genetics clinics and how to refer

GECKO is intended to:

- Facilitate the integration of genomic medicine into practice
- Help health care providers identify and appropriately refer patients who may benefit from genetic services and reassure those at population risk


About Us
Contact Us
Sitemap
GEC KO
Genetics Education Canada - Knowledge Organization
Centre d'éducation en génétique canadien - Connaissances organisées
Search
Point of Care Tools
Educational Resources
Education Modules
Genetics Centres
Public Resources
News & Events
To increase genetics literacy in health care professionals and thereby enhance quality of care in order to optimize the health and well-being of Canadians.
More About us...

My Cancer IQ Web Site – www.mycanceriq.ca

For a cancer risk assessment and personalized action plan